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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
C07D 477/00, 207/12, A61K 31/40, 31/445, 31/495

A1

(11) International Publication Number: WO 94/14811

(43) International Publication Date: 7 July 1994 (07.07.94)

(21) International Application Number: PCT/KR93/00114

(22) International Filing Date: 20 December 1993 (20.12.93)

(30) Priority Data:

1992/24838	21 December 1992 (21.12.92)	KR
1993/09017	25 May 1993 (25.05.93)	KR
1993/12009	30 June 1993 (30.06.93)	KR

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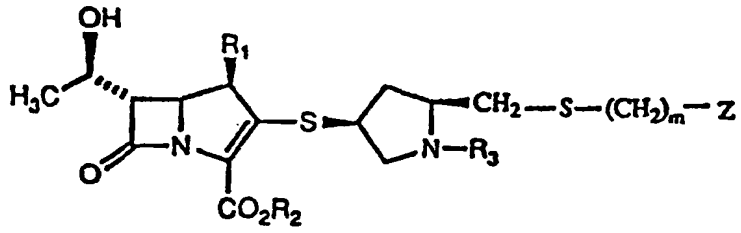
(81) Designated States: AU, BB, BG, BR, BY, CA, CZ, FI, HU, JP, KP, KR, KZ, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: 2-(2-SUBSTITUTED PYRROLIDIN-4-YL)THIO-CARBAPENEM DERIVATIVES



(I)

(a)

(57) Abstract

The present invention relates to novel 2-(2-substituted pyrrolidin-4-yl)-thio-carbapenem derivatives of formula (I), and pharmaceutically acceptable salts thereof, in which R_1 represents hydrogen or (lower)alkyl, R_2 represents hydrogen or anion, R_3 represents hydrogen or (lower)alkanimidoyl, Z represents (a) or Rg, X represents O or NH, and R_4 and R_9 are defined as in claim 1; m is an integer of 1 to 6, provided that when m is 1 and X is 0, R_4 is other than unsubstituted amino(-NH_2), and to a process for preparation of the novel compound of formula (I) and salts thereof, an intermediate for preparation thereof and its prepartion, an antibacterial composition containing the compound (I) and use of the compound (I) as an antibacterial agent.

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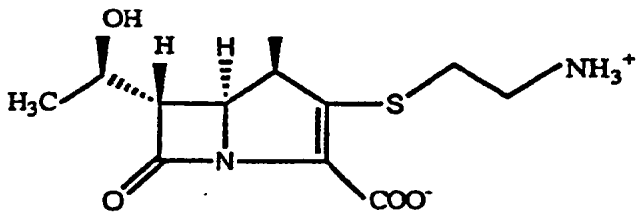
2-(2-SUBSTITUTED PYRROLIDIN-4-YL)THIO-CARBAPENEM DERIVATIVES

TECHNICAL FIELD

The present invention relates to a novel carbapenem derivative useful as a therapeutic agent for treatment of bacterial infectious diseases in pharmacological field.

BACKGROUND ART

Recently, beta-lactam antibiotics having a beta-lactam ring in their structurs as in penicillin derivaties have been discovered in the natural world. As the typical example thereof, thienamycin having the following structural formula was first isolated by fermentation of microorganism Streptomyces cattleya (Journal of American. Assoc. Vol. 100, p6491, 1978).



Thienamycin = [5R-[5α, 6α(R*)]]-3-[(2-aminoethyl)-thio]-6-(1-hydroxyethyl)-7-oxo-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylic acid

According to the result of antimicrobial activity test, it has been identified that thienamycin exhibits a broad and

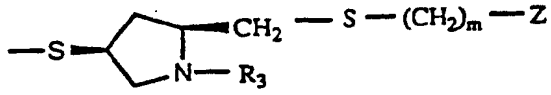
potent antimicrobial activity against gram-positive and gram-negative bacteria. Thus, thienamycin was expected as a beta-lactam antibiotic substance having a high clinical utility. However, it has been reported that since thienamycin itself is chemically unstable and can be readily decomposed in vivo by dehydrogenase-1(DHP-I enzyme) present in kidney, when thienamycin is clinically administered, antibacterial activity in vivo exhibits a tendency to reduce and the recovery rate in urine is extremely low (Antimicro. Agent. Chemother. Vol 22, p62, 1982). Thus, in order to prepare the compound having an improved chemical stability while maintaining a good antibacterial activity of thienamycin numerous thienamycin derivatives have been synthesized. Among such thienamycin derivatives, particularly imipenem, i.e. (5R, 6S, 8R)-3-[[2-(formimidoylamino)ethyl]thio]-6-(1-hydroxyethyl)-7-oxo-1-azabicyclo[3.2.0]hept-ene-2-carboxylic acid hydrate which is prepared by formylating an amino group in thienamycin, exhibits antibacterial activity equivalent to, or higher than, that of thienamycin against various bacteria including beta-lactamase producing strains and particularly a potent antibacterial activity against Pseudomonas aeruginosa, which is 2 to 4 times stronger than that of thienamycin and further shows a slightly improved stability in a solution in comparison withy thienamycin. Accordingly, imipenem was developed as a pharmaceutical medicament which can be practically and clinically utilized (J. Med. Chem. Vol. 22, p1435, 1979). However, since imipenem can be readily decomposed by DHP-I enzyme present in human kidney as like as thienamycin, it cannot be used for treatment of urinary tract infection and further, substances produced by DHP-I enzyme decomposition can induce a serious renal toxicity. Accordingly, imipenem cannot be administered alone and should be administered together with DHP-I enzyme inhibitors such as cilastatin (J. Antimicrob. Chemo. Vol. 12 (Suppl. D) p1(1983)). Moreover, recently a frequent use of imipenem for prophylaxis and treatment of infectious diseases results in remarkable increase of imipenem-resistant Straphylococcus aureus and Pseudomonas aeruginosa strains in

clinical field. Imipenem cannot provide a suitable therapeutic effect on diseases caused by such resistant strains.

As a result of an effort to solve such disadvantages, many antibiotics having chemical structure and pharmacological activity similar to imipenem but not having the above-mentioned disadvantages involved in imipenem have been developed. For example, they are disclosed in European Patent No. 411664A, 272456, 272457, 280771, 341557 and the like. Among these patent specifications, European Patent No. 411664A discloses a carbapenem compound having 2-[2-(aminocarbonyl)vinyl]pyrroldin-4-yl]-thio group at 2-position of a carbapenem basic structure with a specific example of (1R, 5S, 6S)-2-[(2S, 4S)-2-[(E)-2-(aminocarbonyl)vinyl]-pyrrolidin-4-yl-thio]-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid (Bo-2171, compound of Example 3). Such beta-lactam antibiotics generally exhibit a toxic effect selectively only on pathogenic bacteria with substantially no toxic effect on animal cells. Accordingly, they have been broadly and safely used for treatment of infectious diseases caused by bacteria for clinical purpose. However, since these beta-lactam antibiotics do not sufficiently exhibit a satisfactory antibacterial effect on causative microorganisms for incurable infectious disease, such as Staphylococcus aureus and Pseudomonas aeruginosa which are resistant to methicillin, their clinical use is greatly restricted, particularly in immunodeficient patients from which such resistant strains are frequently isolated. Further, although such known antibiotic compounds have a resistance to DHP-I enzyme to some extent, it is not sufficient to the desired extent. Accordingly, the development of antibiotic compounds showing an improved antibacterial activity against such resistant strains has been continuously required. Specifically, the major aspect of development of a novel carbapenem antibiotic compound resides in an increase of resistance against DHP-I enzyme and a reduction of renal toxicity and side effects on central nervous system as well as an increase of antibacterial activity.

DISCLOSURE OF INVENTION

Thus, the present inventors have conducted an extensive study to provide a novel carbapenem compound showing an excellent antibacterial activity and a strong resistance against DHP-I enzyme. As a result, we have found that a novel group of carbapenem compounds having a moiety of the following formula(A) at 2-position of carbapenem structure satisfies the above-mentioned requirement and then completed the present invention :



(A)

wherein

R_3 represents hydrogen or lower alkanimidoyl,

Z represents $-\overset{X}{\overset{\|}{C}}-R_4$ or R_9,

X represents O or NH,

R_4 represents amino or heterocyclic amine group, each of which can be unsubstituted or substituted with a group of formula $-CH\begin{matrix}R_5\\R_6\end{matrix}$, a unsubstituted or substituted heterocyclic group or a lower alkyl group, or represents hydroxy(lower)alkyl or carbamoyloxy(lower)alkyl,

R_5 and R_6 independently of one another represent hydrogen, hydroxy, hydroxy(lower)alkyl, cyano, amino, carbamoyl, carbamoyl(lower)alkyl, cyano(lower)alkyl, mono- or di-(lower)alkylcarbamoyl, carbamoyloxy, ureido, amino(lower)alkyl, carbamoyloxy(lower)alkyl, mono- or di-(lower)alkylcarbamoyl-(lower)alkyl, ureido(lower)alkyl, or a group of formula $-CO-N\bigcirc$ or $-CH_2CO-N\bigcirc$ wherein $-N\bigcirc$ denotes a unsubstituted or substituted 3- to 6-

membered heterocyclic group which can contain additional hetero atoms, provided that R_5 and R_6 cannot be hydrogen at the same time,

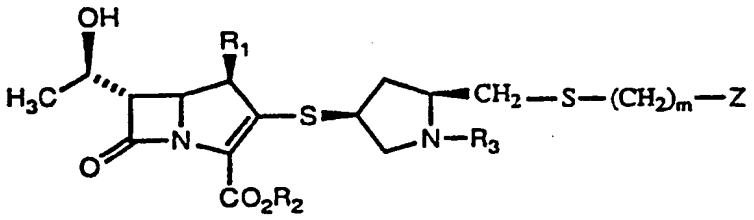
R_9 represents hydroxy(lower)alkyl or carbamoyloxy, and

m is an integer of 1 to 6,

provided that when m is 1 and X is O, R_4 is other than unsubstituted amino($-NH_2$).

A compound of formula (I), as defined below, having the partial structure (A) above is a novel compound which was not disclosed in the prior art up to now. It is identified that the compound (I) exhibits a superior antibacterial activity against both of gram-positive bacteria such as Staphylococcus aureus and gram-negative bacteria such as Pseudomonas aeruginosa and further shows a good stability to DHP-I enzyme.

Accordingly, it is an object of the present invention to provide a novel 2-(2-substituted pyrrolidin-4-yl)thiocarbapenem derivative represented by the following general formula (I) :



(I)

and pharmaceutically acceptable salts thereof, in which

R_1 represents hydrogen or (lower)alkyl,

R_2 represents hydrogen or anion,

R_3 represents hydrogen or (lower)alkanimidoyl,

Z represents $-\overset{X}{\overset{\|}{C}}-R_4$ or R_9,

X represents O or NH,

R_4 represents amino or heterocyclic amine group, each of which can be unsubstituted or substituted with a group of formula $-CH\begin{matrix}R_5\\R_6\end{matrix}$, a unsubstituted or substituted heterocyclic group or a lower alkyl group, or represents hydroxy(lower)alkyl or carbamoyloxy(lower)alkyl,

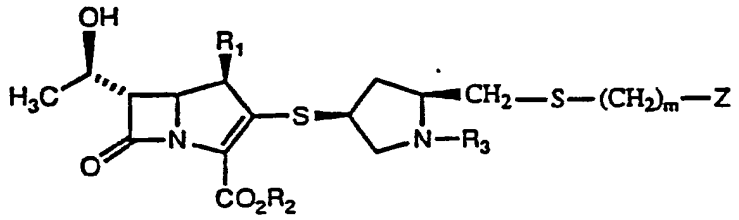
R_5 and R_6 independently of one another represent hydrogen, hydroxy, hydroxy(lower)alkyl, cyano, amino, carbamoyl, carbamoyl(lower)alkyl, cyano(lower)alkyl, mono- or di-(lower)alkylcarbamoyl, carbamoyloxy, ureido, amino(lower)alkyl, carbamoyloxy(lower)alkyl, mono- or di-(lower)alkylcarbamoyl-(lower)alkyl, ureido(lower)alkyl, or a group of formula $-CO-N\bigcirc$ or $-CH_2CO-N\bigcirc$ wherein $-N\bigcirc$ denotes a unsubstituted or substituted 3- to 6-membered heterocyclic group which can contain additional hetero atoms, provided that R_5 and R_6 cannot be hydrogen at the same time,

R_9 represents hydroxy(lower)alkyl or carbamoyloxy, and

m is an integer of 1 to 6, provided that

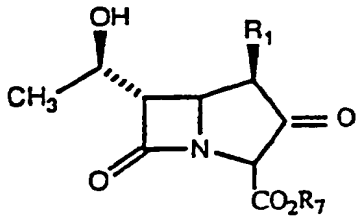
when m is 1 and X is O, R_4 is other than unsubstituted amino($-NH_2$).

Further, it is another object of the present invention to provide a process for preparation of the compound of formula(I) :



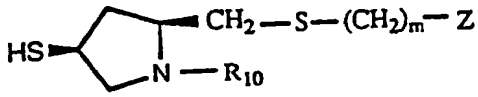
(I)

wherein R_1, R_2, R_3, Z and m are defined as above, or salts thereof, which comprises reacting a compound of formula (II):



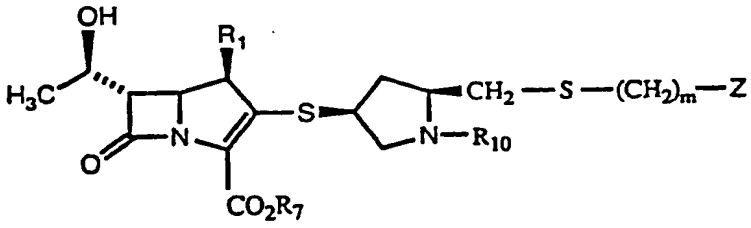
(II)

wherein R_1 is as defined above and R_7 represents a carboxy-protecting group, or a reactive derivative at the oxo group thereof or salts thereof with a compound of formula (III) :



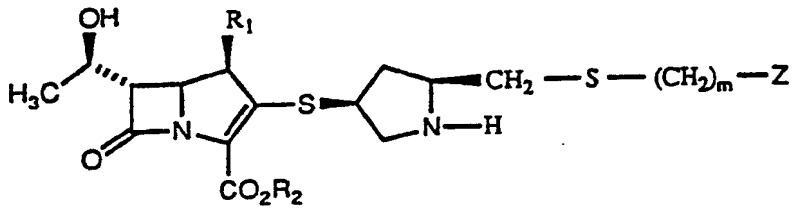
(III)

wherein Z and m are as defined above and R_{10} represents an imino-protecting group, or salts thereof to obtain an intermediate compound of formula (IV),



(IV)

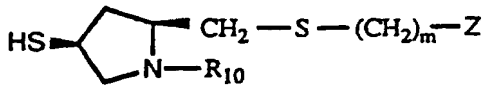
wherein R_1, R_7, R_{10}, Z and m are as defined above, or salts thereof and subjecting the resulting compound of formula (IV) or salts thereof to elimination reaction of the carboxy- and imino-protecting groups and, if necessary, reacting the resulting compound of formula (I-b),



(I-b)

wherein R_1, R_2, Z and m are as defined above, or salts thereof with a lower alkanimidoylating agent.

It is a further object of the present invention to provide a novel 2-substituted mercaptopyrrolidine compound represented by the following general formula (III), which is an intermediate compound useful in the preparation of the desired compound of formula (I) :



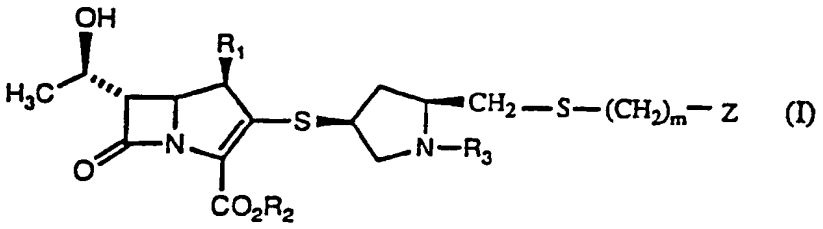
(III)

wherein Z, R_{10} and m are as defined above, and a process for preparation thereof.

Further, it is another object of the present invention to provide a pharmaceutical composition containing a novel carbapenem compound of formula (I) as defined above.

BEST MODE FOR CARRYING OUT THE INVENTION

In one aspect, the present invention relates to a novel 2-(2-substituted pyrrolidin-4-yl)thio-carbapenem derivative of the following general formula (I) :



(I)

and pharmaceutically acceptable salts thereof, in which

R_1 represents hydrogen or (lower)alkyl,

R_2 represents hydrogen or anion,

R_3 represents hydrogen or (lower)alkanimidoyl,

Z represents $-\overset{X}{\overset{\|}{C}}-R_4$ or R_9,

X represents O or NH,

R_4 represents amino or heterocyclic amine group, each of which can beunsubstituted or substituted with a group of formula $-CH\begin{matrix}R_5\\R_6\end{matrix}$, a unsubstituted or substituted heterocyclic group or a (lower)alkyl group, or represents hydroxy(lower)alkyl or carbamoyloxy(lower)alkyl,

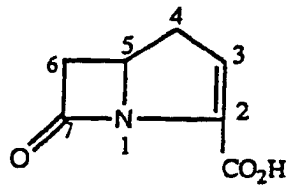
R_5 and R_6 independently of one another represent hydrogen, hydroxy, hydroxy(lower)alkyl, cyano, amino, carbamoyl, carbamoyl(lower)alkyl, cyano(lower)alkyl, mono- or di-(lower)alkylcarbamoyl, carbamoyloxy, ureido, amino-(lower)alkyl, carbamoyloxy(lower)alkyl, mono- or di-(lower)alkylcarbamoyl(lower)alkyl, ureido(lower)alkyl, or a group of formula $-CO-N\bigcirc$ or $-CH_2CO-N\bigcirc$ wherein $-N\bigcirc$ denotes a unsubstituted or substituted 3- to 6-membered heterocyclic group which can contain additional hetero atoms, provided that R_5 and R_6 cannot be hydrogen at the same time,

R_9 represents hydroxy(lower)alkyl or carbamoyloxy, and

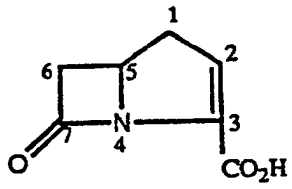
m is an integer of 1 to 6, provided that

when m is 1 and X is O, R_4 is other than unsubstituted amino($-NH_2$).

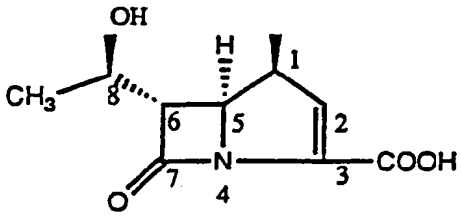
The compound of the present invention has the following basic structure :



This basic structure is named 7-oxo-1-azabicyclo [3.2.0]hept-2-ene-2-carboxylic acid. In the present invention, it is named 1-carbapen-2-em-3-carboxylic acid according to the more generally and widely used nomenclature system for convenience.



The compound of formula (I) according to the present invention includes optical isomers due to asymmetric carbon atoms present in 1-, 5-, 6- and 8-position of the carbapenem moiety and side chain bound to 6-position thereof. Among such isomeric compound, the most preferred compound is a compound having trans configuration (5S, 6S) at 5 and 6 positions, R-configuration at 8-position and R-configuration at lower alkyl group (R_1) present on 1-position, i.e. a compound having the whole configuration (1R, 5S, 6S, 8R).



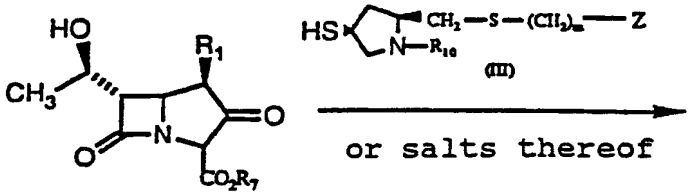
In addition, in a (2-substituted pyrrolidin-4-yl)thio group which is the side chain present on 2-position of the carbapenem structure there may be isomeric compound due to asymmetric carbon atoms present on 2- and 4-positions of pyrrolidine, among which the compound having (2S',4S') or (2R',4R') configuration is most preferable. The compound of formula(I) according to the present invention also includes isomers at pyrrolidine moiety which is the side chain present on 2-position of carbapenem structure.

The desired compound of the present invention also includes a pharmaceutically acceptable salt of the compound of formula(I). Such pharmaceutically acceptable salt may include a base-addition salt such as an inorganic base salt, for example, an alkali metal salt (e.g. sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g. magnesium salt, calcium salt, etc.), etc. or an organic base salt, for example, a salt with an organic base (e.g. triethylamine salt, dicyclohexylamine salt, ethanolamine salt, pyridine salt, picoline salt, etc.); an acid-addition salt such as an inorganic acid addition salt (e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.) or an organic acid addition salt (e.g. formate, acetate, tartrate, benzenesulfonate, etc.); an intermolecular quaternary salt, and the like.

The present invention also provides a process for preparation of 2-(2-substituted pyrrolidin-4-yl)thio-carbapenem derivatives of formula(I) as defined above and salts thereof. The process for preparation of the desired com-

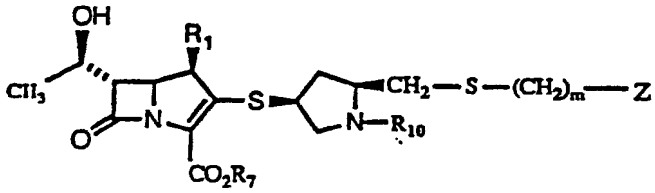
pound of formula(I) according to the present invention can be illustrated by the following reaction scheme:

Process 1)



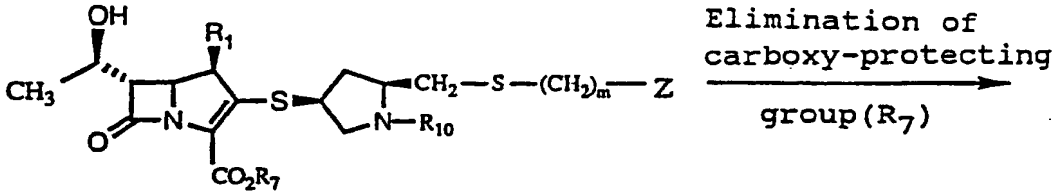
(II) (III) or salts thereof

or a reactive derivative at the oxo group thereof or salts thereof

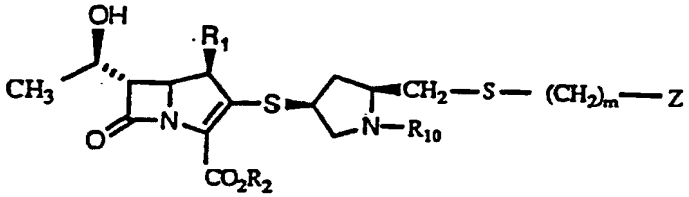


(IV) or salts thereof

Process 2)

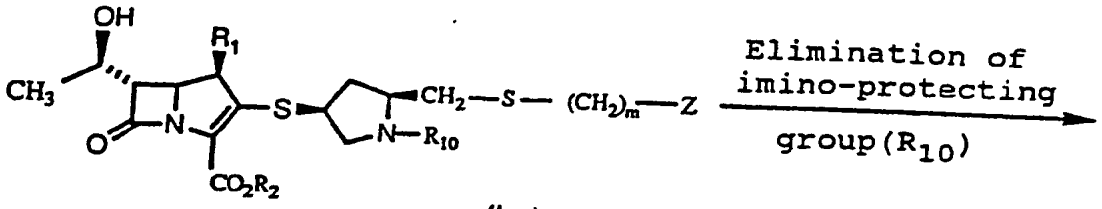


(IV) or salts thereof



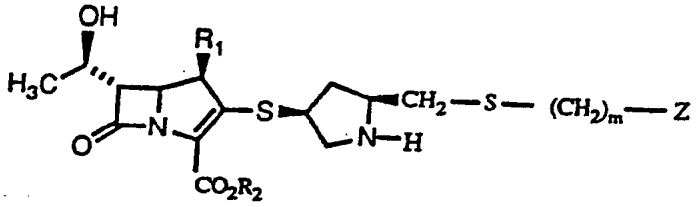
(I-a) or salts thereof

Process 3)



(I-a)

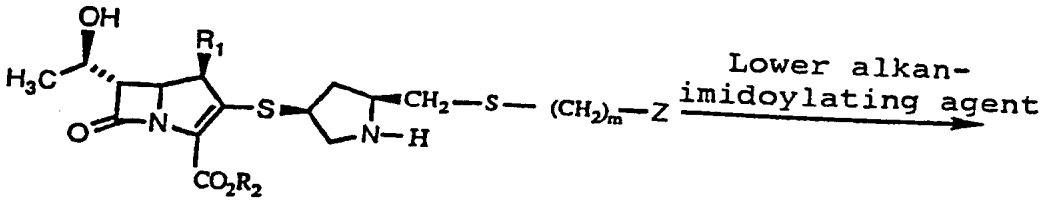
or salts thereof



(I-b)

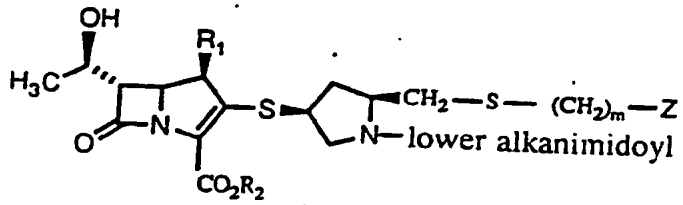
or salts thereof

Process 4)



(I-b)

or salts thereof



(I-c) or salts thereof

In the above reaction scheme,
R_1, R_2, R_3, Z and m are as defined above,
R_7 represents a carboxy-protecting group and
R_{10} represents an imino-protecting group.

The term "lower alkyl" as used herein is intended to mean straight or branched alkyl having 1 to 6 carbon atoms and may include, for example, methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, hexyl, etc. Preferable lower alkyl is methyl, ethyl, propyl or t-butyl, Suitable "carbamoyl(lower)alkyl" may include, for example, carbamoylmethyl, carbamoylethyl, carbamoylpropyl, 1-(carbamoylmethyl)ethyl, 1-carbamoyl-1-methylethyl, carbamoylbutyl, 1,1-dimethyl-2-carbamoylethyl, carbamoylpentyl, carbamoylhexyl, and the like, in which preferable one is carbamoyl-(C_1-C_4)alkyl and the most preferable one is carbamoylmethyl, carbamoylethyl or carbamoylpropyl. Suitable "lower alkanimidoyl" may include straight or branched lower alkanimidoyl having 1 to 6 carbon atoms such as formimidoyl, acetimidoyl, propionimidoyl, butyrimidoyl, isovalerimidoyl, pentanimidoyl, hexanimidoyl, and the like, in which the most preferable one is formimidoyl or acetimidoyl.

Suitable caboxy-protecting group for R_7 may include a group which can form esterified carboxy. Preferable examples of the ester moiety of an esterified carboxy may include lower alkyl ester such as methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester, hexyl ester, etc.; lower alkanoyloxy(lower)alkyl ester which may have suitable substituent(s) such as acetoxymethyl ester, propionyloxymethyl ester, butyryloxymethyl ester, valeryloxymethyl ester, pivaloyloxymethyl ester, hexanoyloxymethyl ester, 1(or 2)-acetoxyethyl ester, 1(or 2, or 3)-acetoxypropyl ester, 1(or 2, or 3, or 4)-acetoxybutyl ester, 1(or 2)-propionyloxy ethyl ester, 1(or 2, or 3)-propionyloxypropyl ester, 1(or 2)-butyryl oxyethyl ester, 1(or 2)-isobutyryloxyethyl ester, 1(or 2)-pivaloyloxy ethyl ester, 1(or 2)-hexanoyloxyethyl

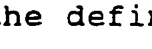
ester, isobutyryloxymethyl ester, (2-ethylbutyryl)oxymethyl ester, (3,3-dimethylbutyryl)oxymethyl ester, 1(or 2)-pentanoyloxyethyl ester, etc.; (lower)alkanesulfonyl(lower)alkyl ester; mono-(or di- or tri-)halo(lower)alkyl ester such as 2-iodoethyl ester, 2,2,2-trichloroethyl ester, etc.; lower alkoxycarbonyloxy(lower)alkyl ester such as methoxycarbonyloxymethyl ester, 2-methoxycarbonyloxyethyl ester, 1-ethoxycarbonyloxyethyl ester, 1-isopropoxycarbonyloxyethyl ester, etc.; phthalidinyl(lower)alkyl ester; (5-lower alkyl-2-oxo-1,3-dioxolan-4-yl)(lower)alkyl ester such as (5-methyl-2-oxo-1,3-dioxolan-4-yl)methyl ester, (5-ethyl-2-oxo-1,3-dioxolan-4-yl)methyl ester, (5-propyl-2-oxo-1,3-dioxolan-4-yl)ethyl ester, etc.; lower alkenyl ester such as vinyl ester, allyl ester, etc.; lower alkynyl ester such as ethynyl ester, propynyl ester, etc.; or aromatic(lower)alkyl ester which may have suitable substituent(s), for example, benzyl ester, 4-methoxybenzyl ester, 4-nitrobenzyl ester, phenylethyl ester, trityl ester, benzhydryl ester, bis(methoxyphenyl)methyl ester, 3,4-dimethoxybenzyl ester, 4-hydroxy-3,5-t-butylbenzyl ester and the like; or aryl ester which may have suitable substituents, for example, phenyl ester, 4-chlorophenyl ester, tosyl ester, t-butylphenyl ester, mesityl ester, cumenyl ester, phthalidyl ester, and the like. Among these ester moieties, particularly preferable one may be substituted aromatic(lower)alkyl ester, most preferably 4-nitrobenzyl or phenyl(C_1-C_4)alkyl ester.

Suitable imino-protecting group for R_{10} may include acyl group such as aliphatic acyl substituted with aromatic or heterocyclic group derived from carboxylic acid, carbonic acid, sulfonic acid or carbamic acid, or carbamoyl, aliphatic acyl, aromatic acyl or heterocyclic acyl. Suitable aliphatic acyl may include saturated or unsaturated acyclic or cyclic acyl groups, for example, lower alkanoyl such as formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, etc.; (lower)alkylsulfonyl such as mesyl, ethylsulfonyl, propylsulfonyl, isopropylsul-

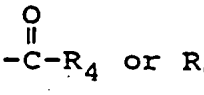
fonyl, butylsulfonyl, isobutylsulfonyl, pentylsulfonyl, hexylsulfonyl, etc.; N-alkylcarbamoyl such as methylcarbamoyl, ethylcarbamoyl, etc.; (lower)alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, t-butoxycarbonyl, etc.; (lower)alkenyloxycarbonyl such as vinyloxycarbonyl, allyloxycarbonyl, etc.; (lower) alkenoyl such acryloyl, methacryloyl, crotonoyl, etc.; cyclo(lower)alkylcarbonyl such as cyclopentylcarbonyl, cyclopropylcarbonyl, cyclohexylcarbonyl, etc., and the like. Suitable aromatic acyl may include heterocyclic carbonyl such as furoyl, thienylcarbonyl, nicotinoyl, isonicotinoyl, thiazolylcarbonyl, thiadiazolylcarbonyl, tetrazolylcarbonyl, etc. The aliphatic acyl substituted with aromatic group may include aralkanoyl such as phenyl(lower)alkanoyl, for example, phenylacetyl, phenylpropionyl, phenylhexanoyl, etc.; aralkoxycarbonyl such as phenyl(lower)alkoxycarbonyl, for example, benzyloxycarbonyl, phenylethyloxycarbonyl, etc.; aryloxyalkanoyl such as phenoxy(lower)alkanoyl, for example, phenoxyacetyl, phenoxypropionyl, etc., and the like. The aliphatic acyl substituted with heterocyclic group may include heterocyclic(lower)alkanoyl such as thienylacetyl, imidazolylacetyl, pyridylacetyl, tetrazolylacetyl, thiazolylacetyl, thiadiazolylacetyl, thienylpropionyl, thiadiazolylpropionyl, tec. The above-mentioned acyl groups may have one or more substituent(s) and the preferable example of suitable substituent is as follows: (lower)alkyl such as methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, etc.; halogen such as chlorine, bromine, iodine, fluorine, etc.; (lower)alkoxy such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentyloxy, hexyloxy, etc.; (lower)alkylthio such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, pentylthio, hexylthio, etc.; mono-(or di- or tri-)haloalkanoyl such as chloroacetyl, bromoacetyl, dichloroacetyl, trifluoroacetyl, etc.; mono-(or di- or tri-)haloalkoxycarbonyl such as chloromethoxycarbonyl, dichloromethoxycarbonyl, 2,2,2-trichloro-ethoxycarbonyl, etc.; or nitro(or halo or lower alkoxy)aryl-oxycarbonyl such as nitrobenzyloxycarbonyl, chlorobenzyloxycarbonyl, methoxybenzyloxycar-

bonyl, etc., and the like. More preferable example of imino-protecting groups as defined above may be (C_2-C_4)alkenyloxycarbonyl or phenyl(C_1-C_4)alkoxycarbonyl which may have nitro substituent, and the most preferable one may be allyloxycarbonyl or 4-nitrobenzyloxycarbonyl.

Suitable "lower alkylene" may include, for example, methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, methylmethylene, ethylethylene, propylene, etc., in which more preferable example may be C_1-C_4 alkylene and the most preferable one may be methylene.

In the definitions of R_5 and R_6 above,  denotes a 3- to 6-membered heterocyclic group which may contain additional hetero atoms, preferably nitrogen atom, such as substituted or unsubstituted aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl or piperazinyl, in which the preferable substituent may be carbamoyl, (lower)alkyl, hydroxy(lower)alkyl, cyano(lower)alkyl, amino(lower)alkyl, carbamoyloxy(lower)alkyl or amino.

"Substituted or unsubstituted heterocyclic amine" suitable for R_4 preferably means a N-containing heterocyclic group, particularly aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl or piperazinyl, which may be unsubstituted or substituted with carbamoyl, (lower)alkyl, hydroxy(lower)alkyl, cyano(lower)alkyl, amino(lower)alkyl, carbamoyloxy(lower)alkyl, ureido(lower)alkyl, carbamoyl(lower)alkyl, or mono or di-(lower)alkylcarbamoyl(lower)alkyl.

Among 2-(2-substituted pyrrolidin-4-yl)thio-carbapenem compounds of formula(I) according to the present invention, the preferable one is the compounds wherein R_1 represents hydrogen or lower alkyl, R_2 represents hydrogen or anion, R_3 represents hydrogen or straight or branched (C_1-C_6)alkanimidoyl, Z represents  or R_9, R_4 represents  ,

wherein R_5 and R_6 independently of one another represent hydrogen, hydroxy, hydroxy(lower)alkyl, CN, carbamoyl(lower)alkyl, cyano(lower)alkyl, carbamoyloxy(lower)alkyl, ureido(lower)alkyl or substituted or unsubstituted piperazinyl provided that R_5 and R_6 cannot be hydrogen at the same time, R_9 represents hydroxy(C_1-C_6)alkyl or carbamoyloxy and m is an integer of 1 to 4.

Particularly preferable compounds of formula(I) according to the present invention are the compounds wherein R_1 represents methyl, R_2 represents hydrogen, R_3 represents hydrogen or acetimidoyl, Z represents $-\overset{O}{\overset{\|}{C}}-R_4$ or R_9, R_4 represents $-NHCH\begin{matrix}R_5\\R_6\end{matrix}$, wherein R_5 and R_6 independently of one another represent hydrogen, hydroxy, hydroxy(C_1-C_4)alkyl, cyano, cyano(C_1-C_4)alkyl, carbamoyloxy(C_1-C_4)alkyl, ureido(C_1-C_4) alkyl, or piperazinyl optionally mono-substituted with substituent selected from carbamoyl, (C_1-C_4)alkyl, hydroxy(C_1-C_4)alkyl, cyano(C_1-C_4)alkyl, amino(C_1-C_4)alkyl, carbamoyloxy(C_1-C_4)alkyl, ureido(C_1-C_4)alkyl, carbamoyl(C_1-C_4)alkyl and mono- or di-(C_1-C_4)alkylcarbamoyl(C_1-C_4)alkyl, provided that R_5 and R_6 cannot be hydrogen at the same time, R_9 represents hydroxy(C_1-C_4)alkyl or carbamoyloxy and m is an integer of 1 to 2.

The following example can be mentioned as the most preferable compound of formula(I) according to the present invention :

-(1R,5S,6S)-2-[(2S,4S)-2-{(cyanomethylcarbamoyl)methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{(cyanomethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{(aminoethylcarbamoyl)ethylmercap-

tomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{(carbamoylmethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{(hydroxyethylcarbamoyl)methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{(carbamoylmethylcarbamoyl)methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{(cyanoethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{(hydroxyethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{(carbamoylethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-1-acetimidoyl-2-{(2-carbamoylethylcarbamoyl)methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-1-acetimidoyl-2-{(2-carbamoylmethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{(1,2-dihydroxyethylcarbamoyl)methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{(1-hydroxy-2-cyanoethylcarbamoyl)-methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{(1-hydroxy-2-aminoethylcarbamoyl)-methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{(1-hydroxy-2-carbamoylethylcarbamoyl)methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{(1,2-dihydroxyethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{(1-hydroxy-2-cyanoethylcarbamoyl)-ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{(1-hydroxy-2-carbamoylethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{(1-(hydroxymethyl)-2-hydroxyethylcarbamoyl)methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-{[2S,4S)-2-{(1-(hydroxymethyl)-2-carbamoylethylcarbamoyl)methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{(1-(hydroxymethyl)-2-carbamoylethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{(1-(carbamoylmethyl)-2-ureidoethylcarbamoyl)methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{(1-(carbamoylmethyl)-2-cyanoethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{(1-(carbamoylmethyl)-2-aminoethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{(2-ureidoethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{(N-methylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{(N,N-dimethylcarbamoyl)methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-

methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{1-acetimidoyl-2-(carbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{1-acetimidoyl-2-(N-methylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{(N-(2-hydroxyethyl)-piperazinylcarbonyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{(N-(2-carbamoyloxyethyl)-piperazinylcarbonyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{(N-(2-aminoethyl)-piperazinylcarbonyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{(2-hydroxyethyl)mercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{(3-hydroxypropyl)mercaptomethyl}-pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{(3-(carbamoyloxy)propyl)mercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{2-(hydroxyethylpiperidinylcarbonylmethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{2-(aminoethylpiperidinylcarbonylmethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{2-(methoxyethylpiperidinylcarbonylmethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{2-(carbamoyloxyethylpiperidinylmethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{2-(ureidoethylpiperidinylmethyl carbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{2-(methoxymethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{2-(carbamoyloxymethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{2-(ureidomethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{2-(methoxymethyloxymethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{2-(aminomethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{2-(cyanoethylpiperidinylcarbonylmethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{2-(methylcarbamoyloxymethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{2-(methoxymethyloxyethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

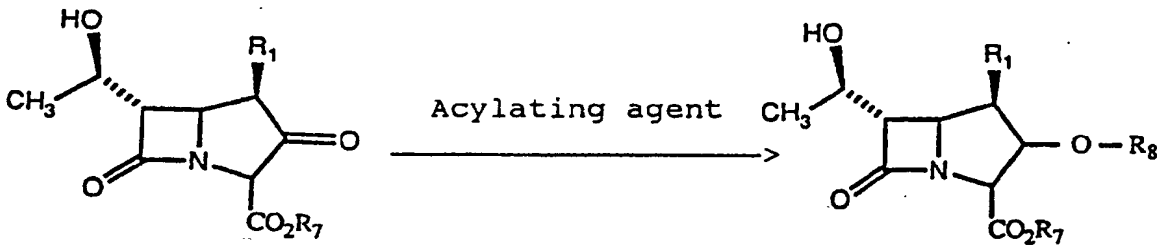
-(1R,5S,6S)-2-[(2S,4S)-1-formimidoyl-2-{(hydroxyethylcarbonyl)methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid, and

-(1R,5S,6S)-2-[(2S,4S)-2-{(carbamoylethyl)mercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid.

The novel desired compound of formula(I) according to the present invention can be prepared by the processes as illustrated by Processes 1 to 4 above. The processes are explained in detail in the following.

(1) Process 1 :

In Process 1 of the method according to the present invention, a carbapenem derivative of formula(II) or a reactive derivative at the oxo group thereof or a salt thereof is reacted with a mercaptopyrrolidine derivative of formula(III) or a salt thereof to prepare a compound of formula(IV) or a salt thereof. In this reaction, the carbapenem derivative of formula(II) can be preferably converted into a reactive derivative of formula(II-a) which is then reacted with the mercaptopyrrolidine derivative of formula(III). Such reactive derivative can be prepared by reacting the compound of formula(II) with an acylating agent as illustrated in the following reaction scheme :



(II) (II-a)

or salts thereof or salts thereof

In the above reaction scheme, R_1 and R_7 are as defined above, R_8 represents acyl group as exemplified for the imino-protecting group R_{10} or 0,0-substituted phosphono group derived from, for example, organic phosphoric acid as mentioned below.

Suitable acylating agent which can be used in the above

reaction may include conventional ones which can introduce the acyl group as mentioned above into the compound(II). Preferable acylating agents may be organic sulfonic acid, organic phosphoric acid, or its reactive derivative such as acid halide or acid anhydride, for example, arenesulfonyl halide such as benzenesulfonyl chloride, p-toluenesulfonyl chloride, p-nitrobenzenesulfonyl chloride, p-bromobenzenesulfonyl chloride, etc.; arenesulfonic anhydride such as benzenesulfonic anhydride, p-toluenesulfonic anhydride, p-nitrobenzenesulfonic anhydride, etc.; optionally halogen-substituted(lower)alkanesulfonyl halide such as methanesulfonyl chloride, ethanesulfonyl chloride, trifluoromethane sulfonyl chloride, etc.; optionally halogen-substituted (lower)alkanesulfonic anhydride such as methanesulfonic anhydride, ethanesulfonic anhydride, trifluoromethanesulfonic anhydride, etc.; di(lower)alkyl phosphorohaloridate such as diethyl phosphorochloridate, etc.; diaryl phosphorohaloridate such as diphenyl phosphorochloridate, etc., and the like, with diphenyl phosphorochloridate being most preferable.

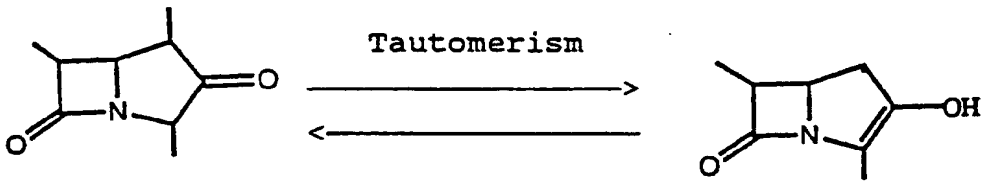
This acylation reaction for converting the compound of formula(II) into the reactive derivative of formula(II-a) is preferably carried out in the presence of a solvent. For this purpose, any conventional organic solvent which does not adversely influence the reaction, for example, acetone, dioxane, acetonitrile, chloroform, dichloromethane, benzene, toluene, hexamethylphosphoramide, dichloroethane, tetrahydrofuran, ethyl acetate, dimethylsulfoxide, N,N-dimethylformamide, pyridine, etc., can be used. Particularly, the most preferable solvent may be acetonitrile or benzene.

When the acylating agent is used in the form of a free acid or its salt in this acylation reaction, the reaction is usually carried out in the presence of a condensing agent. Suitable condensing agent for this purpose may include, for example, carbodiimide compounds such as N,N-diethylcarbodiimide, N,N-diisopropylcarbodiimide, N,N-dicyclohexylcarbo-

diimide, N-cyclohexyl-N'-morpholinoethylcarbodiimide, N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide, N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide, etc.; imidazole compounds such as N,N'-carbonyldiimidazole, N,N'-carbonylbis(2-methylimidazole), etc.; keteneimine compounds such as pentamethyleneketene-N-cyclohexylimine, diphenylketene-N-cyclohexylimine, etc.; 1-alkoxy-1-chloroethylene; ethoxyacetylene; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride; phosphorus trichloride; thienyl chloride; oxalyl chloride; a combination of triphenylphosphine with carbon tetrachloride or diazenedicarboxylate; 2-ethyl-7-hydroxybenzeneisoxazolium salt, and the like, with N,N'-carbonyldiimidazole being most preferable. In addition, this acylation reaction may be practiced in the presence of an inorganic or organic base. Suitable bases for this purpose may include hydroxides, carbonates, bicarbonates or alkanoates of an alkali metal such as lithium, sodium, potassium, etc., and an alkaline earth metal such as calcium, magnesium, etc., for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium acetate, magnesium carbonate or calcium carbonate; or tri(lower)alkyl amine such as triethylamine, trimethylamine, N,N-diisopropyl-N-ethylamine, etc.; pyridine compounds such as pyridine, picoline, lutidine, etc.; N,N-di(lower)alkylaminopyridine; N-(lower)alkylmorpholine; N,N-di(lower)alkylbenzeneamine, and the like. The most preferable base is N,N-diisopropylethylamine or triethylamine.

The acylation reaction is generally carried out under cooling to warming, for example, at the temperature of -40°C to 50°C, preferably at the temperature of -20°C to 20°C. The reaction time is generally in the range of 0.5 to 3 hours, preferably in the range of 1 to 2 hours. In this acylation reaction, 1 to 3 moles, preferably 1 to 1.5 moles, of the base and 1 to 3 moles, preferably 1 to 1.5 moles of the acylating agent are generally used with respect to one mole of the compound of formula(II).

With regard to the compound(II), it is well known that the 3,7-dioxo-1-azabicyclo[3.2.0]heptane ring system of the following formula(II-b) lies in tautomeric relation with the 3-hydroxy-7-oxo-1-azabicyclo[3.2.0]hept-2-one ring system of the following formula(II-c). Accordingly, it should be understood that both of these ring systems are substantially the same.



(II-b) (II-c)

The compound of formula(II) or the compound of formula(II-a) or salts thereof can be subsequently reacted with the compound of formula(III) or salts thereof to prepare the intermediate compound of formula(IV) or salts thereof. In this reaction, the compound of formula(II-a) produced by the above acylation reaction can be used with or preferably without isolation. The reaction of the compound (II) or (II-a) or salts thereof with the compound(III) or salts thereof can be carried out in a reaction-inert solvent which does not adversely influence the reaction. As an example of such solvent, those solvent given in the explanation of the acylation reaction may be mentioned. The most preferable one may be acetonitrile or benzene. The reaction temperature can be varied within a substantially wide range. Generally, the reaction is carried out under cooling to warming.

(2) Process 2 :

In Process 2, the compound(IV) or salts thereof subjected to elimination reaction of the carboxy-protecting group R_7 to prepare the compound(I-a) or salts thereof. The present reaction for removing the carboxy-protecting group is usually carried out by means of a conventional method such as hydrolysis, reduction, and the like.

(i) Hydrolysis

Hydrolysis for removing the carboxy-protecting group is preferably carried out in the presence of an acid or a base.

Suitable acid which can be used in such acid hydrolysis reaction may include an organic acid such as formic acid, acetic acid, propionic acid, trifluoroacetic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.; and an inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, etc. When the acidic hydrolysis is carried out using trifluoroacetic acid, the reaction can be accelerated by addition of a cation-trapping agent such as phenol, anisol, etc.

Suitable base for the basic hydrolysis may include an alkali metal hydroxide such as sodium hydroxide, potassium hydroxide, etc.; an alkaline earth metal hydroxide such as magnesium hydroxide, calcium hydroxide, etc.; an alkaline earth metal hydride such as calcium hydride, etc.; an alkali metal hydride such as sodium hydride, etc; an alkali metal alkoxide such as sodium methoxide, sodium ethoxide, potassium t-butoxide, etc.; an alkali metal carbonate such as sodium carbonate, potassium carbonate, etc.; or an alkali metal bicarbonate such as sodium bicarbonate, potassium bicarbonate, etc., and the like.

This hydrolysis reaction is usually carried out in the presence of a solvent which does not adversely influence the reaction such as water, alcohol, for example, methanol, ethanol, etc., tetrahydrofuran, and the like, in which the preferable one may be methanol. When the acid or base used

in the hydrolysis is a liquid form, it can be also used as the solvent.

(ii) Reduction

The reduction method which can be used for elimination reaction of the carboxy-protecting group may include reduction by using a combination of a metal such as zinc or zinc amalgam or a salt of chrome compound such as chromous chloride or chromous acetate and an organic or inorganic acid such as acetic acid, propionic acid, hydrochloric acid, sulfuric acid, etc.; and conventional catalytic reduction in the presence of a conventional metallic catalyst such as palladium catalyst, for example, spongy palladium, palladium black, palladium oxide, palladium on carbon, palladium hydroxide on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc., nickel catalysts, for example, reduced nickel, nickel oxide, Raney nickel, etc., or patinum catalyst, for example, platinum plate, platinum black, platinum on carbon, colloidal platinum, platinum oxide, etc., and the like. Among those reduction methods, the catalytic reduction using palladium oxide or palladium on carbon is most preferable. In case that the catalytic reduction is applied, the reaction is preferably carried out under neutral condition.

This reduction can be conveniently carried out in a solvent which does not adversely influence the reaction. For this purpose, suitable solvent may include, for example, water, alcohol such as methanol, ethanol, propanol, etc., dioxane, tetrahydrofuran, acetic acid, phosphate buffer, and the like, or a mixture thereof, with the mixed solvent of water and ethanol or water and tetrahydrofuran being most preferable. In this reaction, the preferable reaction temperature is in the range of 0°C to 30°C, most preferably in the range of 20°C to 30°C, and the reaction time is generally 0.5 to 4 hours and most preferably 2 to 3 hours. The amount of catalyst used in this reduction is usually

0.01 to 1 moles, preferably 0.01 to 0.5 moles, with respect to one mole of the compound of formula(IV). Hydrogen atmosphere is used in 1 to 4 atmospheric pressure and preferably in 3 to 4 atmospheric pressure.

In case that the carboxy-protecting group is allyl group, it can be deprotected by hydrogenolysis in the presence of a palladium compound. Suitable palladium compound used in this deprotecting reaction may include palladium on carbon, palladium hydroxide on carbon, palladium chloride, tetrakis(triphenylphospine)palladium (0), bis (dibenzylidenylacetone)palladium(0), di[(1,2-bis(diphenylphosphino)ethane]palladium(0), tetrakis(triphenylphosphite) alladium(0), tetrakis(triethylphosphite)palladium(0). This reaction can preferably be carried out in the presence of a scavenger of allyl group generated in situ. Suitable scavenger which can be used for this purpose may include, for example, amine such as morpholine, N-methylaniline, etc.; an activated methylene compound such as dimedone, benzoylacetate, 2-methyl-3-oxovaleric acid, etc.; a cyanohydrin compound such as α-tetrahydropyranyloxybenzylcyanide, etc.; lower alkanoic acid such as formic acid, ammonium formate, sodium acetate, etc.; N-hydroxysuccinimide, and the like. This reaction can also be carried out in the presence of a base such as lower alkylamine, for example, butylamine, triethylamine, etc., pyridine, and the like. When palladium-ligand complex is used in this reaction, the reaction can preferably be carried out in the presence of the corresponding ligand, for example, triphenylphosphine, triphenylphosphite, triethylphosphite, and the like. The reaction is usually carried out in a reaction-inert solvent such as water, methanol, ethanol, propanol, dioxane, tetrahydrofuran, acetonitrile, chloroform, dichloromethane, dichloroethane, ethylacetate, etc. The reaction temperature can be varied within a substantially wide range and the reaction is generally carried out under cooling to warming.

The elimination reaction of protecting group can be

carried out using a reducing agent appropriately selected depending on the kind of carboxy-protecting group to be eliminated.

(3) Process 3 :

In the reaction of Process 3, the compound of formula(I-a) or salts thereof is subjected to elimination reaction of the imino-protecting group(R_{10}) to prepare the compound of formula(I-b) or salts thereof. This elimination reaction of the imino-protecting group can generally be carried out by means of a conventional method such as hydrolysis, reduction, and the like. The method of hydrolysis and reduction, and the reaction conditions (reaction temperature, solvent, and the like) are substantially the same as those illustrated for elimination reaction of the carboxy-protecting group in Process 2 above. If necessary, the reaction of Process 3 can be directly carried out in the same reaction vessel without isolation of the compound(I-a) produced by Process 2.

The reaction of Process 3 for removing the imino-protection group is carried out in the same manner as the reaction of Process 2 for removing the carboxy-protecting group.

Alternatively, Process 3 can be practiced simultaneously with Process 2 and this case is also included within the scope of the present invention.

(4) Process 4 :

In Process 4, the compound of formula(I-b) or salts thereof is reacted with lower alkanimidoylating agent to prepare the compound of formula(I) wherein R_3 is lower alkanimidoyl group, i.e. the compound of formula(I-c), or salts thereof.

In this reaction, suitable lower alkanimidoylating agent may be any of conventional ones which can introduce the lower alkanimidoyl group into the compound of formula (I-b). As a specific example of such lower alkanimidoylating agent, the following compounds can be mentioned : lower alkyl(lower)alkanimidate such as methyl formimidate, ethyl formimidate, methyl acetimidate, ethyl acetimidate, ethyl propionimidate, methyl butyrimidate, ethyl isovalerimidate, ethyl pentanimidate, ethyl hexanimidate, etc.; lower alkanimidoyl halide such as formimidoyl chloride, formimidoyl bromide, acetimidoyl chloride, acetimidoyl bromide, propionimidoyl bromide, butyrimidoyl chloride, isovalerimidoyl chloride, pentanimidoyl chloride, hexanimidoyl chloride, etc., and the like, with methyl formimidate or methyl acetimidate being most preferable.

This reaction is usually carried out in a solvent which does not adversely influence the reaction such as tetrahydrofuran, dioxane, water, methanol, ethanol, etc., or a mixture thereof. The most preferable solvent may be a mixed solvent of water and ethanol. The reaction temperature can be varied within a substantially wide range and the reaction is generally carried out under cooling to warming, most preferably at the temperature of -10°C to 10°C, for the reaction time of 0.5 to 3 hours, more preferably 1 to 1.5 hours.

In the present reaction, the lower alkanimidoylating agent may be used in an amount of 1 to 2 moles, preferably 1 to 1.5 moles and particularly 1.2 moles, with respect to one mole of the compound(I-b).

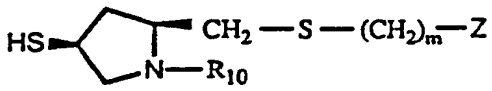
The reaction can also be carried out in the presence of an inorganic or organic base. Suitable base which can be used in this reaction may be those given in the explanation of the reaction of Process 1. In this reaction, the base is used in an amount sufficient to maintain the pH value of the reaction solution at the weak alkaline level, preferably in

the range of pH 8 to 9 and most preferably in the range of pH 8.5 to 8.7.

The compound of formula(I) and salts thereof obtained from the Processes 1 to 4 according to the present invention can be isolated and purified by means of a conventional manner, for example, extraction, precipitation, fractional crystallization, recrystallization, column chromatography, and the like.

Suitable salts of the compounds of formulae(II), (II-a), (III), (IV), (I-a), (I-b) and (I-c), which are used as starting materials and reactants or obtained as reaction products in the Processes 1 to 4 above, may be the same as those specifically exemplified in connection with the salts of the compound of formula(I).

The mercaptopyrrolidine derivative of formula(III), which is used as a reactant in Process 1 above for preparation of the compound(I) according to the present invention, is a novel compound which was never disclosed in the prior art. Accordingly, another object of the present invention is to provide a compound of the following formula(III) :



(III)

or salts thereof, in which

R_{10} represents an imino-protecting group,

Z represents $-\overset{\overset{X}{\|}}{C}-R_4$ or R_9,

X represents O or NH,

R_4 represents amino or heterocyclic amine group, each of which can be unsubstituted or substituted with a group of formula $-CH(R_5)(R_6)$, a unsubstituted or substituted heterocyclic group or a (lower)alkyl group, or represents hydroxy(lower)alkyl or carbamoyloxy(lower)alkyl,

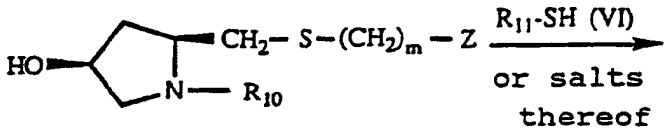
R_5 and R_6 independently of one another represent hydrogen, hydroxy, hydroxy(lower)alkyl, cyano, amino, carbamoyl, carbamoyl(lower)alkyl, cyano(lower)alkyl, mono- or di-(lower)alkylcarbamoyl, carbamoyloxy, ureido, amino(lower)alkyl, carbamoyloxy(lower)alkyl, mono- or di-(lower)alkylcarbamoyl(lower)alkyl, ureido(lower)alkyl, or a group of formula -CO-N◯ or $-CH_2$CO-N◯ wherein -N◯ denotes a unsubstituted or substituted 3- to 6-membered heterocyclic group which can contain additional hetero atoms, provided that R_5 and R_6 cannot be hydrogen at the same time,

R_9 represents hydroxy(lower)alkyl or carbamoyloxy, and

m is an integer of 1 to 6, provided that when m is 1 and X is O, R_4 is other than unsubstituted amino($-NH_2$).

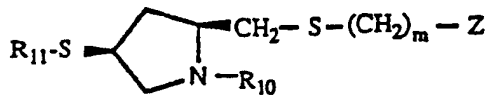
Further, the present invention provides a process for preparation of the compound of formula(III) and salts thereof. The process for preparation of the compound(III) according to the present invention can be represented by Methods A and B as depicted below.

Method A



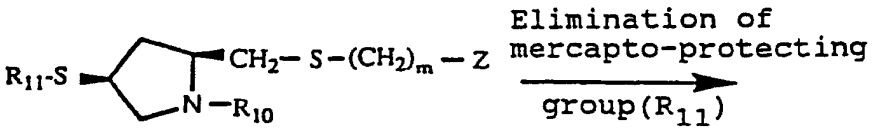
(V)

or a reactive derivative
at the hydroxy group thereof
or salts thereof

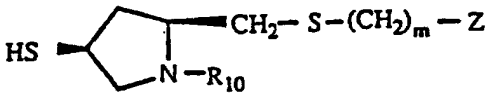


or salts thereof (III-a)

Method B



or salts thereof (III-a)



or salts thereof (III)

In the above reaction scheme, R_{11} represents a mercapto-protecting group, and R_{10}, Z and m are as defined above.

Suitable "mercapto-protecting group" for R_{11} may in-

clude acyl group as mentioned above in connection with the imino-protecting group; ar(lower)alkyl group such as mono- or di- or tri-phenyl(lower)alkyl, for example, benzyl, phenethyl, benzhydryl, trityl, etc.; and the like, in which more preferable example may be C_1-C_4 alkanoyl, aroyl and triphenyl(C_1-C_4)alkyl and the most preferable mercapto-protecting group may be acetyl.

Methods A and B for preparing the novel compound of formula(III) and salts thereof are explained in detail in the following.

a) Method A :

In Method A, the compound of formula(V) or a reactive derivative at the hydroxy group thereof or salts thereof can be reacted with the mercaptan derivative of formula(VI) or salts thereof to prepare the derivative of formula(III-a) or salts thereof.

Suitable reactive derivative at the hydroxy group of the compound of formula(V) may include a conventional one such as halides, for example, chloride, bromide, iodide, etc.; sulfonates, for example, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.; and the like, with a sulfonate compound, particularly methanesulfonate being most preferable. In case that the compound of formula(V) is a methanesulfonate derivative, the reaction of Method A can be carried out, for example, by reacting one equivalent weight of the compound of formula(VI) with 1 to 2 equivalent weight, preferably 1.2 equivalent weight, of the methanesulfonate compound of formula(V) and 1 to 2 equivalent weight, preferably 1.2 equivalent weight, of an organic or inorganic base in a halogenated alkane solvent such as dichloromethane, at the temperature of -10°C to 40°C, more preferably -5°C to 0°C, for 1 to 3 hours, more preferably 1 to 1.5 hours.

Preferable example of the mercaptan derivative of formula(VI) used as a reactant in the reaction of Method A may be ar(lower)alkanethiol such as mono- or di- or triphenyl(lower)alkanethiol, for example, phenylmethanethiol, diphenylmethanethiol, triphenylmethanethiol, etc.; thio(lower)alkanoic-S-acid such as thioacetic-S-acid, etc.; thioarenoic-S-acid such as thiobenzoic-S-acid, etc.; and the like, in which more preferable example may be triphenyl(C_1-C_4)alkanethiol, thio(C_1-C_4)alkanoic-S-acid and thio(C_6-C_{10})-arenoic-S-acid, and salts thereof. The most preferable mercaptan derivative(VI) may be thioacetic-S-acid or its potassium salt. In case that the compound(VI) is thioacetic-S-acid potassium salt, the reaction of Method A can be carried out in a stoichiometric manner, for example, by reacting one equivalent weight of the compound(V) with 1 to 2 equivalent weight, preferably 1.5 equivalent weight, of potassium thioacetate(VI) in a solvent such as dimethylsulfoxide, hexamethylphosphoramide or N,N-dimethylformamide, preferably in N,N-dimethylformamide, at the temperature in the range of 60°C to 100°C, more preferably 80°C to 90°C, for 2 to 5 hours, more preferably 2.5 to 3 hours.

In Method A, when the compound of formula(VI) is ar(lower)alkanethiol, the compound of formula(V) is preferably used in the form of its reactive derivative at the hydroxy group and the reaction can be conveniently carried out in the presence of an inorganic or organic base. Suitable inorganic or organic base used in this reaction may be those exemplified in Process 1 above.

In case that the compound(VI) is thio(lower)alkanoic-S-acid or thioarenoic-S-acid, the reaction of Method A is preferably carried out in the presence of a conventional condensing agent such as a combination of triarylphosphine, for example, triphenylphosphine, etc., and di(lower)alkylazodicarboxylate, for example, diethylazodicarboxylate, etc. This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction,

such as dichloromethane, methanol, ethanol, propanol, pyridine, N,N-dimethylformamide or tetrahydrofuran, with tetrahydrofuran being most preferable. In such a case, the reaction of Method A is preferably carried out, for example, by reacting one equivalent weight of the compound of formula(V) with 1 to 2 equivalent weight, preferably 1.5 equivalent weight, of thio(lower)alkanoic-S-acid such as thioacetic acid, 1 to 2 equivalent weight, preferably 1.5 equivalent weight, of diethylazodicarboxylate and 1 to 5 equivalent weight, preferably 2 equivalent weight, of triphenylphosphine in tetrahydrofuran solvent at the temperature of -40°C to 10°C, preferably 0°C to 5°C, for 2 to 5 hours, preferably 2 to 3 hours.

As a result of the reaction of Method A, the configuration on the carbon atom substituted with the hydroxy group of the compound(V) is inverted in the resulting compound (III-a).

b) Method B :

In Method B, the compound of formula(III-a) or salts thereof obtained from Method A is subjected to elimination reaction of the mercapto-protecting group to prepare the compound of formula(III) or salts thereof.

The elimination reaction of the mercapto-protecting group according to Method B is carried out by means of a conventional method as described below and can be appropriately selected depending on the kind of the mercapto-protecting group to be eliminated. For example, when the protecting group is ar(lower)alkyl group, this protecting group can generally be eliminated by treating with a silver compound such as silver nitrate, silver carbonate, etc. This elimination reaction with silver compound is preferably carried out in the presence of an organic base such as pyridine, etc. The resulting silver salt of the compound of formula(III) can be converted into its alkali metal salt, if

necessary, by treating with alkali metal halide such as sodium iodide, potassium iodide, etc.

Further, in case that the mercapto-protecting group is acyl, this protecting group can generally be eliminated by solvolysis such as alcoholysis or hydrolysis using acid or base. Suitable acid and base which can be used in this reaction may be those exemplified in connection with hydrolysis in Process 2 above, in which sodium methoxide and sodium hydroxide is most preferable. This hydrolysis is usually carried out in a conventional solvent which does not adversely influence the reaction such as alcohol, for example, methanol, ethanol, etc., water, pyridine, N,N-dimethylformamide, etc., or a mixture thereof, in which the most preferable one is methanol or water.

In case that the reaction of Method B is carried out by basic hydrolysis, the reaction is carried out, for example, by using 1 to 2 moles, preferably 1 to 1.5 moles, of a base with respect to one mole of the compound of formula(III-a) in the presence of a solvent such as water, alcohol or tetrahydrofuran, most preferably in methanol solvent, at the temperature of -20°C to 50°C, most preferably -10°C to 10°C, for 0.5 to 2 hours, most preferably 0.5 to 1 hour. The reaction is practiced substantially in a stoichiometric manner.

The compound of formula(III) obtained from Methods A and B above can be isolated and purified according to a conventional method, for example, by extraction, precipitation, fractional crystallization, recrystallization, chromatography, and the like.

The novel carbapenem derivative of formula(I) and pharmaceutically acceptable salts thereof according to the present invention exhibit a potent antibacterial activity against various gram-positive and gram-negative bacterial strains and, therefore, has a clinical utility for prophy-

laxis and treatment of various bacterial infectious diseases. Antibacterial activity of the desired compound(I) of the present invention is demonstrated by the following experiments including in vitro antibacterial activity test.

Test Examples

Test 1 : In vitro antibacterial activity test

The antibacterial activity of the compound(I) of the present invention was determined by measuring the minimal inhibitory concentration(MIC) according to the antibacterial activity test method as described below. The compounds of Examples 1,2,3 and 4 according to the present invention were used as a test compound and imipenem was used as a comparative compound.

The test compounds and comparative compound were gradually diluted in Mueller Hinton Agar(MHA) medium. Test strains as listed in the following table were inoculated into the medium in an amount of 10^6 viable cells/ml and then incubated at 37°C for 18 hours. Then, MIC value was measured and expressed in terms of μg/ml. The results are shown in the following Table 1.

Table 1. Minimal Inhibitory Concentration of the compound(I) and imipenem

MICs / Test compound / Test strains	Minimal Inhibitory Concentration (μg/ml)				
	Imipenem	Example 1	Example 2	Example 3	Example 4
Staphylococcus aureus SG 511	0.10	0.05	0.05	0.05	0.05
Escherichia coli DC 2	0.78	0.10	0.10	0.10	0.10
Escherichia coil TEM	0.20	0.10	0.05	0.05	0.10
Pseudomonas aeruginosa 9027	0.78	0.10	0.78	0.39	0.10
Pseudomonas aeruginosa 1592E	0.78	0.78	0.78	0.39	0.78
Salmonella typhimurium	0.78	0.20	0.10	0.10	0.20
Klebsiella aerogenes 1522E	0.78	0.20	0.10	0.10	0.10
Klebsiella oxytoca 1082E	0.39	0.20	0.20	0.20	0.20
Enterobacter cloacae 1321E	0.20	0.05	0.05	0.05	0.05

From the result given in Table 1 above, it can be seen that the compound of formula(I) and pharmaceutically acceptable salts thereof according to the present invention exhibit a considerably superior antibacterial activity in com-

parison with the known compound in the prior art, imipenem.

Test 2 : Stability test against kidney dehydrogenase DHP-I

Each of the novel compounds of Examples 1,2,3 and 4 of the present invention and the comparative compound imipenem was dissolved in 10mM phosphate buffer and the resulting solution was mixed with dehydrogenase enzyme solution extracted from pig kidney in a ratio of equivalent amounts. The resulting mixture was incubated at 37°C for 2 hours, during which the decomposition degree of the compound was measured. The result thereof was given in the following Table 2 in terms of percentage of the remaining amount on the basis of the initially added amount of the compound.

Table 2. Stability of the compounds(I) and imipenem on DHP-I enzyme

(Unit:%)

Test Compound \ Time(minute)	5	10	20	40	80	120
Imipenem	99.2	97.9	94.3	87.7	77.0	66.6
Compound of Example 1	99.7	99.4	99.1	98.1	97.5	97.2
Compound of Example 2	100	99.4	98.6	97.2	96.3	96.3
Compound of Example 3	99.7	99.2	98.9	98.0	97.2	97.0
Compound of Example 4	100	99.8	99.0	98.8	98.8	98.8

From the result given in Table 2 above, it can be seen that the known compound in prior art, imipenem, was decom-

posed by about 40% within about 2 hours from the begining of mixing incubation, while the novel compound of formula(I) of the present invention was substantially never decomposed and shows a high stability. Such test result demonstrates that imipenem has a disadvantage in that it should be administered together with an enzyme inhibitor such as Cilastatin, whereas the compound of the present invention shows stably a high antibacterial activity even when it is administered alone.

As can be demonstrated by the results of Tests 1 and 2 above, the carbapenem derivative of formula(I) and pharmaceutically acceptable salts thereof according to the present invention are clinically used for the purpose of prophylaxis and treatment of infectious diseases. For this purpose, the compound of formula(I) and pharmaceutically acceptable salts thereof can be formulated into a pharmaceutically acceptable preparation suitable for administration, together with pharmaceutically acceptable carriers such as solid or liquid excipients. Such pharmaceutical preparation may be in solid or liquid form, for example, tablet, capsule, granule, powder, pill, solution, suspension, syrup, emulsion, and the like. If necessary, the pharmaceutical preparation can additionally contain conventional additives, for example, formulating aid, stabilizer, wetting agent, thickening agent, disintegrator, perfume, pigment, binder, and the like.

The dosage of the compound of formula(I) and pharmaceutically acceptable salts thereof according to the present invention may vary depending on kind and severity of diseases to be treated, age and conditions of the patient, and kind of the compound(I) to be administered. In general, an amount of 100 to 500mg per day may be administered per one adult patient as a single dose or a multiple-divided dose.

The present invention will be explained by the following Examples and Reference Examples in more detail. Howev-

er, it should be understood that the present invention is not limited by these examples in any manner.

Example 1

Preparation of (1R,5S,6S)-2-[(2S,4S)-2-{(cyanomethylcarbamoyl)methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

(1) 580mg of 4-nitrobenzyl-2-diphenoxyphosphoryloxy-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate and 380mg of (2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-{(cyanomethylcarbamoyl)methylmercaptomethyl}-4-mercaptopyrrolidine were dissolved in 25ml of acetonitrile. To the resulting solution was added dropwise 0.25ml of N,N-diisopropylethylamine under nitrogen atmosphere at -10°C to -5°C and then the reaction mixture was stirred overnight at 5°C. The reaction solution was concentrated under reduced pressure. 20ml of 5% sodium bicarbonate solution was added to the residue and the mixture was extracted with 30ml of ethylacetate. The extract was dried over magnesium sulfate and concentrated under reduced pressure. The residue was subjected to column chromatography(eluent: EtOAc:acetone=3:2 v/v) to obtain 760mg of 4-nitrobenzyl (1R,5S,6S)-2-[(2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-{(cyanomethylcarbamoyl)methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate.

IR(Nujol)cm^{-1}: 1755, 1751, 1710, 1653

NMR($CDCl_3$)δ: 1.27(3H,d,J=8Hz), 1.37(3H,d,J=8Hz), 1.78-1.90(1H,m), 2.30-2.80(7H,m), 3.31-3.76(4H,m), 5.04-5.54(6H,m), 7.44-7.50(2H,dd,J=18Hz), 7.55-7.65(4H,d,J=9Hz), 8.17-8.25(6H,m)

(2) 690mg of the compound obtained in the above (1) was dissolved in 10ml of tetrahydrofuran. To the resulting

solution were added 18ml of 0.1M 4-morpholinopropane sulfonate solution (pH=7.0), 1.8ml of ethanol and 0.3g of 10% palladium on carbon and then the mixture was hydrogenated under pressure. After the reaction time of 4 hours, the catalyst was filtered off and the filtrate was washed with 20ml of dichloromethane. The aqueous layer was separated and purified with polymer chromatography(CHP-20, eluent: 5%THF-H_2O). Then, the eluate was lyophilized to obtain 170mg of the title compound.

Melting Point : 173-174.5°C (dec.)
IR(KBr)cm^{-1} : 1750, 1580, 1390
NMR(D_2O) δ : 1.20(3H,d,J=8Hz), 1.28(3H,d,J=8Hz), 1.40-2.10(2H,m), 2.55-3.95(6H,m)

Example 2

Preparation of (1R,5S,6S)-2-[(2S,4S)-2-{(cyanomethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

(1) The reaction was carried out in the same manner as that of Example 1-(1), starting from 480mg of 4-nitrobenzyl-2-diphenoxyphosphoryloxy-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate and 320mg of (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-{(cyanomethylcarbamoyl)ethylmercaptomethyl}-4-mercapto]pyrrolidine to obtain 580mg of 4-nitrobenzyl (1R,5S,6S)-2-[(2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-{(cyanomethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate.

IR(Nujol)cm^{-1} : 1780, 1750, 1620
NMR(D_2O) δ : 1.21(3H,d,J=8Hz), 1.30(3H,d,J=8Hz), 3.02-3.85(12H,m), 4.80(2H,br. s), 5.25(2H,s), 5.38(2H,dd,J=18Hz),

7.58(2H,d,J=8Hz), 8.26(6H,m)

(2) The compound obtained in the above (1) was hydrogenated in the same manner as that of Example 1-(2) to obtain 120mg of the title compound.

Melting Point : 175-175.5°C (dec.)
IR(KBr)cm^{-1} : 1750, 1580
NMR(D_2O) δ : 1.23(3H,d,J=7.9Hz), 1.30(3H,d,J=6.8Hz), 1.81(1H,dd,J=18Hz,J=8.5Hz), 2.70-3.34(5H,m), 3.45-3.85(3H,m), 4.25-4.27(2H,m)

Example 3

Preparation of (1R,5S,6S)-2-[(2S,4S)-2-{(hydroxyethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

(1) The reaction was carried out in the same manner as that of Example 1-(1), starting from 550mg of 4-nitrobenzyl-2-diphenoxyphosphoryloxy-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate and 410mg of (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-{(hydroxyethylcarbamoyl)ethylmercaptomethyl}-4-mercapto]pyrrolidine to obtain 420mg of 4-nitrobenzyl (1R,5S,6S)-2-[(2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-{(hydroxyethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate.

IR(Nujol)cm^{-1} : 3400, 1770-1740, 1710-1680, 1605
NMR($CDCl_3$) δ : 1.1-1.6(6H,m), 5.1-5.6(4H,m), 7.3-7.7(4H,m), 8.21(4H,d,J=9Hz)

(2) The compound obtained in the above (1) was hydrogenated in the same manner as that of Example 1-(2) to obtain 250mg of the title compound.

Melting Point : 172-173°C (dec.)
IR(KBr)cm^{-1} : 1765-1725, 1590-1550
NMR(D_2O) δ : 1.21(3H,d,J=8Hz), 1.28(3H,d,J=7Hz), 1.52-2.0(4H,m), 2.49-2.9(3H,m)

Example 4

Preparation of (1R,5S,6S)-2-[(2S,4S)-2-{(2-carbamoylmethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

(1) The reaction was carried out in the same manner as that of Example 1-(1), starting from 650mg of 4-nitrobenzyl-2-diphenoxyphosphoryloxy-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate and 350mg of (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-{(2-carbamoylmethylcarbamoyl)ethylmercaptomethyl}-4-mercapto]pyrrolidine to obtain 450mg of 4-nitrobenzyl (1R,5S,6S)-2-[(2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-{(2-carbamoylmethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate.

IR(Nujol)cm^{-1} : 1770, 1705, 1610, 1525
NMR($CDCl_3$) δ : 1.25(3H,d,J=7.5Hz), 1.32(3H,d,J=6Hz), 3.10-4.83(3H,m), 4.81(2m,br. s), 5.24(2H,s), 5.38(2H,dd,J=18Hz), 7.56-7.68(4H,dd,J=18Hz), 8.24(4H,d,J=8Hz)

(2) The compound obtained in the above (1) was hydrogenated in the same manner as that of Example 1-(2) to obtain 120mg of the title compound.

Melting Point : 168-172°C (dec.)
IR(KBr)cm^{-1} : 1755, 1680
NMR(D_2O) δ : 1.21(3H,d,J=9Hz), 1.27(3H,d,J=6Hz),

1.42-2.03(2H,m), 2.53-4.36(10H,m)

Example 5

Preparation of (1R,5S,6S)-2-[(2S,4S)-1-acetimidoyl-2-{(2-carbamoylmethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

120mg of the compound obtained in Example 4-(2), (1R,5S,6S)-2-[(2S,4S)-2-{(2-carbamoylmethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-{(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid was dissolved in 30ml of distilled water. To the resulting solution was added 1.4g of ethylacetimidate hydrochloride. Then, the reaction mixture was adjusted to pH 8.4-8.6 by adding 10% aqueous sodium carbonate solution at 0 to 4°C. When the reaction was completed, the reaction mixture was adjusted to pH 6.5 by adding 1N-aqueous hydrochloric acid solution and then washed with the mixture of 50ml of ethyl acetate and 10ml of tetrahydrofuran. The organic layer was removed and the aqueous layer was subjected to polymer chromatography (CHP-20, eluent : 5% acetone-H_2O). The eluate was lyophilized to obtain 80mg of the title compound.

IR(KBr)cm^{-1} : 1800-1720

NMR(D_2O) δ : 1.27(6H,t,J=7.4Hz), 2,30-2.80(3H,s)

Example 6

Preparation of (1R,5S,6S)-2-[(2S,4S)-2-{(carbamoyl-1-(hydroxy)ethylcarbamoyl)methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

(1) The reaction was carried out in the same manner as that of Example 1-(1), starting from 580mg of 4-nitrobenzyl-2-diphenoxyphosphoryloxy-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate and 310mg of (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-{(carbamoyl-1-(hydroxy)ethylcarbamoyl)methylmercaptomethyl}-4-mercapto]pyrrolidine to obtain 620mg of 4-nitrobenzyl (1R,5S,6S)-2-[(2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-{(carbamoyl-1-(hydroxy)ethylcarbamoyl)methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate.

IR(Neat)cm^{-1} : 1765, 1725-1700, 1605
NMR($CDCl_3$) δ : 1.1-1.7(6H,m), 5.0-5.6(4H,m), 7.4-7.8(4H,m), 8.21(4H,d,J=8.5Hz)

(2) The compound obtained in the above (1) was hydrogenated in the same manner as that of Example 1-(2) to obtain 170mg of the title compound.

Melting Point : 176-177.5°C (dec.)
IR(KBr)cm^{-1} : 1765, 1705-1675
NMR(D_2O) δ : 1.21(3H,d,J=9Hz), 1.27(3H,d,J=6Hz), 1.42-2.03(2H,m), 2.53-4.36(10H,m)

Example 7

Preparation of (1R,5S,6S)-2-[(2S,4S)-2-{(hydroxy-1-(hydroxymethyl)ethylcarbamoyl)methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

(1) The reaction was carried out in the same manner as that of Example 1-(1), starting from 720mg of 4-nitrobenzyl-2-diphenoxyphosphoryloxy-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate and 310mg of (2S,4S)-[1-(p-ni-

trobenzyloxycarbonyl)-2-{(hydroxy-1-(hydroxymethyl)ethylcarbamoyl)methylmercaptomethyl}-4-mercapto]pyrrolidine to obtain 840mg of 4-nitrobenzyl (1R,5S,6S)-2-[(2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-{(hydroxy-1-(hydroxymethyl)ethylcarbamoyl)methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate.

IR(Nujol)cm^{-1} : 1760, 1725-1710, 1705, 1605
NMR($CDCl_3$) δ : 1.26(3H,d,J=9Hz), 1.36(3H,d,J=6Hz), 5.15-5.45(6H,m), 7.40-7.75(6H,m), 8.25(6H,d,J=8Hz)

(2) The compound obtained in the above (1) was hydrogenated in the same manner as that of Example 1-(2) to obtain 225mg of the title compound.

Melting Point : 168-171°C (dec.)
IR(Nujol)cm^{-1} : 1750, 1725-1700, 1580
NMR(D_2O) δ : 1.22(3H,d,J=7Hz), 1.28(3H,d,J=6Hz), 1.6-1.9(2H,m), 2.49-2.90(2H,m)

Example 8

Preparation of (1R,5S,6S)-2-[(2S,4S)-2-{(carbamoyl-1-(hydroxymethyl)ethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]-thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

(1) The reaction was carried out in the same manner as that of Example 1-(1), starting from 760mg of 4-nitrobenzyl-2-diphenoxyphosphoryloxy-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate and 350mg of (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-{(carbamoyl-1-(hydroxymethyl)ethylcarbamoyl}-4-mercapto]pyrrolidine to 840mg of 4-nitrobenzyl (1R,5S,6S)-2-[(2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-{(carbamoyl-1-(hydroxymethyl)ethylcarbamoyl)ethylmercaptomethyl}-

pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate.

IR(Nujol)cm^{-1} : 1765, 1725, 1710, 1690
NMR($CDCl_3$) δ : 1.23(3H,d,J=9Hz), 1.33(3H,d,J=8Hz), 4.42-4.56(2H,m), 4.82-5.5(10H,m), 7.4-7.70(4H,m), 8.25(6H,d,J=8Hz)

(2) The compound obtained in the above (1) was hydrogenated in the same manner as that of Example 1-(2) to obtain 250mg of the title compound.

Melting Point : 163-167°C (dec.)
IR(KBr)cm^{-1} : 1750, 1725-1710
NMR(D_2O) δ : 1.22(3H,d,J=7Hz), 1.28(3H,d,J=6Hz), 1.45-2.00(4H,m), 2.46-2.95(3H,m), 3.01-3.13(3H,m)

Example 9

Preparation of (1R,5S,6S)-2-[(2S,4S)-2-{(2-cyano-1-(carbamoylmethyl)ethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

(1) The reaction was carried out in the manner as that of Example 1-(1), starting from 820mg of 4-nitrobenzyl-2-diphenoxyphosphoryloxy-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate and 380mg of (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-{(cyano-1-(carbamoylmethyl)ethylcarbamoyl)ethylmercaptomethyl}-4-mercapto]pyrrolidine to obtain 920mg of 4-nitrobenzyl(1R,5S,6S)-2-[(2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2{(cyano-1-(carbamoylmethyl)ethylcarbamoyl)-ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate.

IR(Nujol)cm^{-1} : 1765, 1715-1705, 1665
NMR($CDCl_3$) δ : 1.18(3H,d,J=9Hz), 1.26(3H,d,J=9Hz), 5.15-5.47(6H,m), 7.40-7.75(6H,m), 8.25(6H,d,J=8Hz)

(2) The compound obtained in the above (1) was hydrogenated in the same manner as that of Example 1-(2) to obtain 270mg of the title compound.

Melting Point : 163-164°C (dec.)
IR(Nujol)cm^{-1} : 1750, 1725-1705, 1665
NMR($CDCl_3$) δ : 1.22(3H,d,J=7Hz), 1.28(3H,d,J=6Hz), 1.60-1.90(2H,m), 2.50-3.10(4H,m)

Example 10

Preparation of (1R,5S,6S)-2-[(2S,4S)-2-{(carbamoylethyl)mercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

(1) The reaction was carried out in the same manner as that of Example 1-(1), starting from 520mg of 4-nitrobenzyl-2-diphenoxyphosphoryloxy-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate and 270mg of (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2{(carbamoylethyl)mercaptomethyl}-4-mercapto]pyrrolidine to obtain 480mg of 4-nitrobenzyl (1R,5S,6S)-2-[(2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-{(carbamoylethyl)mercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate.

IR(Nujol)cm^{-1} : 1775-1760, 1690-1660
NMR($CDCl_3$) δ : 1.26(3H,d,J=7Hz), 1.33(3H,d,J=7Hz), 1.70-2.15(2H,m), 2.30-2.80(2H,m), 4.50-4.83(4H,m), 7.40-7.65(4H,m), 8.25(6H,d,J=8Hz)

(2) The compound obtained in the above (1) was hydrogenated in the same manner as that of Example 1-(2) to obtain 120mg of the title compound.

Melting Point : 162-163°C (dec.)
IR(KBr) cm^{-1} : 1765, 1715-1690, 1580
NMR(D_2O) δ : 1.27(3H,d,J=8Hz), 1.33(3H,d,J=8Hz), 2.17-2.50(4H,m), 2.65-2.95(2H,m)

Example 11

Preparation of (1R,5S,6S)-2-[(2S,4S)-2-{(hydroxyethyl)mercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

(1) The reaction was carried out in the same manner as that of Example 1-(1), starting from 480mg of 4-nitrobenzyl-2-diphenoxyphosphoryloxy-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate and 210mg of (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-{(hydroxyethyl)-mercaptomethy}-4-mercapto]pyrrolidine to obtain 325mg of 4-nitrobenzyl(1R,5S,6S)-2-[(2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-{(hydroxyethyl)mercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate.

IR(Neat) cm^{-1} : 3400, 1765-1725, 1610-1590
NMR($CDCl_3$) δ : 1.20-1.80(6H,m), 5.1-5.6(4H,m), 7.3-7.70(4H,m), 8.20(4H,d,J=8Hz)

(2) The compound obtained in the above (1) was hydrogenated in the same manner as that of Example 1-(2) to obtain 80mg of the title compound.

Melting Point : 172-174°C (dec.)
IR(KBr) cm^{-1} : 1760-1730, 1595-1775
NMR(D_2O) δ : 1.21(3H,d,J=8Hz), 1.28(3H,d,J=7Hz),

1.51-2.1(1H,m), 2.99-2.9(1H,m)

Example 12

Preparation of (1R,5S,6S)-2-[(2S,4S)-2-{(4-(2-hydroxyethyl) piperazinyl)carbonylethylmercaptomethyl}pyrrolidin-4-yl] thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

(1) The reaction was carried out in the same manner as that of Example 1-(1), starting from 720mg of 4-nitrobenzyl-2-diphenoxyphosphoryloxy-6-{(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate and 250mg of (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-{(4-(2-hydroxyethyl)piperazinyl)carbonyethylmercaptomethy}-4-mercapto]pyrrolidine to obtain 870 mg of 4-nitrobenzyl(1R,5S,6S)-2-[(2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-{(4-2-hydroxyethyl)piperazinyl)carbonylethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate.

IR(Neat)cm^{-1} : 3400, 1760-1750, 1690, 1525
NMR($CDCl_3$) δ : 1.26(3H,d,J=6Hz), 1.33(3H,d,J=6Hz), 1.80-2.18(4H,m), 2.27-2.38(4H,m), 5.10-5.63(4H,m), 7.48(2H,d,J=8Hz), 7.62(2H,d,J=8Hz), 8.16-8.27(4H,d,J=8Hz)

(2) The compound obtained in the above (1) was hydrogenated in the same manner as that of Example 1-(2) to obtain 210mg of the title compound.

Melting Point : 168-170°C (dec.)
IR(KBr)cm^{-1} : 3400, 1760-1735, 1600-1580
NMR(D_2O) δ : 1.23(3H,d,J=8Hz), 1.28(3H,d,J=8Hz), 1.45-1.85(2H,m), 2.30-2.66(3H,m), 2.88-3.0(3H,m)

Example 13

Preparation of (1R,5S,6S)-2-[(2S,4S)-2-{(4(2-hydroxyethyl) piperazinylcarbonylmethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

(1) The reaction was carried out in the same manner as that of Example 1-(1), starting from 680mg of 4-nitrobenzyl-2-diphenoxyphosphoryloxy-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate and 290mg of (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-{((4-(2-hydroxyethyl)piperazinylcarbonylmethylcarbamoyl)ethylmercaptomethy}-4-mercapto]-pyrrolidine to obtain 580mg of 4-nitrobenzyl(1R,5S,6S)-2-[(2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-{((4-(2-hydroxyethyl)piperazinylcarbonylmethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate.

IR(Neat)cm^{-1} : 3400, 1770, 1705, 1650
NMR($CDCl_3$) δ : 1.25(3H,d,J=7.5Hz), 1.32(3H,d,J=6Hz), 2.21-2.38(2H,m), 3.10-4.83(4H,m), 4.85(2H,br. s), 5.24(2H,s), 7.52(2H,d,J=8Hz), 7.65(2H,d,J=8Hz), 8.25(4H,d,J=8Hz)

(2) The compound obtained in the above (1) was hydrogenated in the same manner as that of Example 1-(2) to obtain 90mg of the title compound.

Melting Point : 180-182°C (dec.)
IR(KBr)cm^{-1} : 3400, 1755, 1680
NMR(D_2O) δ : 1.22(3H,d,J=8Hz), 1.30(3H,d,J=8Hz), 1.57-2.35(6H,m), 3.01-3.55(2H,m)

Example 14

Preparation of (1R,5S,6S)-2-[(2S,4S)-2-{(aminocarbonyloxymethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

(1) The reaction was carried out in the same manner as that of Example 1-(1), starting from 420mg of 4-nitrobenzyl-2-diphenoxyphosphoryloxy-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate and 280mg of (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-{(aminocarbonyloxymethylcarbamoyl)-ethylmercaptomethy}-4-mercapto]pyrrolidine to obtain 380mg of 4-nitrobenzyl(1R,5S,6S)-2-[(2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-{(aminocarbonyloxymethylcarbamoyl)ethylmercaptomethyl}-pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate.

IR(Neat)cm^{-1} : 3400, 1765, 1725-1715, 1610-1600, 1512, 1360

NMR($CDCl_3$) δ : 1.1-1.6(6H,m), 4.25-5.8(6H,m), 7.4-8.2(4H,m), 8.15(4H,d,J=8.5Hz)

(2) The compound obtained in the above (1) was hydrogenated in the same manner as that of Example 1-(2) to obtain 110mg of the title compound.

Melting Point : > 170°C (dec.)

IR(KBr)cm^{-1} : 1750, 1700-1690, 1600-1580

NMR(D_2O) δ : 1.23(3H,d,J=7.0Hz), 1.29(3H,d,J=6Hz), 1.6-2.1(2H,m), 2.5-3.0(2H,m)

Example 15

Preparation of (1R,5S,6S)-2-[(2S,4S)-2-{2-(ureidomethylcar-

bamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

(1) The reaction was carried out in the same manner as that of Example 1-(1), starting from 580mg of 4-nitrobenzyl-2-diphenoxyphosphoryloxy-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate and 275mg of (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-{2-(ureidomethylcarbamoyl)ethylmercaptomethy}-4-mercapto]pyrrolidine to obtain 425mg of 4-nitrobenzyl(1R,5S,6S)-2-[(2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-{2-(ureidomethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate.

IR(Neat)cm^{-1} : 3400, 1775, 1710-1690, 1610, 1525-1510, 1350

NMR($CDCl_3$) δ : 1.25-1.35(6H,m), 3.05-4.25(10H,m), 4.80(2H,br. s), 5.20(2H,s), 5.40(2H,dd,J=14Hz), 7.56(2H,d,J=8Hz), 7.68(2H,d,J=8Hz), 8.26(4H,d,J=8Hz)

(2) The compound obtained in the above (1) was hydrogenated in the same manner as that of Example 1-(2) to obtain 90mg of the title compound.

Melting Point : > 175°C (dec.)

IR(KBr)cm^{-1} : 1760, 1710, 1650, 1580

NMR(D_2O) δ : 1.21(3H,d,J=9Hz), 1.28(3H,d,J=6Hz), 1.42-2.10(4H,m), 2.53-4.36(14H,m)

Example 16

Preparation of (1R,5S,6S)-2-[(2S,4S)-2-{2-(aminomethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

(1) The reaction was carried out in the same manner as that of Example 1-(1), starting from 620mg of 4-nitrobenzyl-2-diphenoxyphosphoryloxy-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate and 380mg of (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-{2-((4-nitrobenzyloxycarbonyl)methylcarbamoyl)ethylmercaptomethyl}-4-mercapto]pyrrolidine to obtain 420mg of 4-nitrobenzyl (1R,5S,6S)-2-[(2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-{2-((4-nitrobenzyloxycarbonyl)methylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate.

IR(Nujol)cm^{-1} : 1765-1700, 1710-1690, 1660-1650, 1530-1510

(2) The compound obtained in the above (1) was hydrogenated in the same manner as that of Example 1-(2) to obtain 190mg of the title compound.

Melting Point : > 180°C (dec.)
IR(Nujol)cm^{-1} : 1760-1750, 1590-1580, 1350
NMR(D_2O) δ : 1.21(3H,d,J=7Hz), 1.30(3H,d,J=7Hz), 1.40-2.1(4H,m), 2.55-3.08(4H,m), 3.12-4.35(9H,m)

Example 17

Preparation of (1R,5S,6S)-2-[(2S,4S)-2-{2-(methoxymethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

(1) The reaction was carried out in the same manner as that of Example 1-(1), starting from 510mg of 4-nitrobenzyl-2-diphenoxyphosphoryloxy-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate and 250mg of (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-{2-(methoxymethylcarbamoyl)ethylmercaptomethy}-4-mercapto]pyrrolidine to obtain 420mg of 4-

nitrobenzyl (1R,5S,6S)-2-[(2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-{2-(methoxymethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate.

IR(Nujol)cm^{-1} : 1750, 1700, 1685, 1516

NMR($CDCl_3$) δ : 1.28(3H,d,J=7Hz), 1.37(3H,d,J=7Hz), 1.65-2.10(3H,m), 2.35-2.85(2H,m), 2.94(3H,s), 5.25(4H,s), 5.40-5.75(2H,m), 7.56(2H,d,J=9Hz), 7.66(2H,d,J=9Hz), 8.26(4H,d,J=9Hz)

(2) The compound obtained in the above (1) was hydrogenated in the same manner as that of Example 1-(2) to obtain 110mg of the title compound.

Melting Point : > 178°C (dec.)

IR(KBr)cm^{-1} : 1760-1750, 1590-1580, 1350

NMR(D_2O) δ : 1.22(3H,d,J=7Hz), 1.28(3H,d,J=6Hz), 1.45-2.10(4H,m), 2.24-2.95(2H,m), 3.13(3H,s)

The compounds of the following Examples 18 to 27 can be prepared in the same manner as that of Example 1 using the corresponding starting materials.

Example 18

(1) (1R,5R,6S)-2-[(2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-{2-((4-cyanoethylpiperazinyl)carbonylmethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

IR(Neat)cm^{-1} : 3600, 1765, 1710-1685, 1610, 1520

NMR($CDCl_3$) δ : 1.30-1.38(6H,dd,J=18Hz), 2.25-2.83(7H,m), 3.18-3.50(3H,m), 5.20-5.52(4H,m), 7.56-7.69(4H,m), 8.28(4H,d,J=9Hz)

(2) (1R,5S,6S)-2-[(2S,4S)-2-{2-((4-cyanoethylpiperazinyl)carbonylmethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

$UV_{max}^{H_2O}$: 298.2nm
IR(Nujol) cm^{-1} : 1755, 1710, 1585
NMR(D_2O) δ : 1.22(3H,d,J=6Hz), 1.31(3H,d,J=6Hz), 1.75-2.35(5H,m)

Example 19

(1) (1R,5S,6S)-2-[(2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-{2-((4-p-nitrobenzyloxycarbonylaminoethylpiperazinyl)carbonylmethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]-thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

IR(Neat) cm^{-1} : 1765-1750, 1710, 1660-1640, 1530-1510
NMR($CDCl_3$) δ : 1.30(3H,d,J=7Hz), 1.38(3H,d,J=7Hz), 1.75-2.10(3H,m), 2.80-3.90(10H,m), 3.90-4.40(4H,m), 5.20-5.50(6H,m), 7.55(4H,d,J=8Hz), 7.66-8.25(4H,dd)

(2) (1R,5S,6S)-2-[(2S,4S)-2-{2-((4-aminoethylpiperazinyl)carbonylmethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]-thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

$UV_{max}^{H_2O}$: 297.8nm
IR(Nujol) cm^{-1} : 1750, 1590-1580
NMR(D_2O) δ : 1.22(5H,d,J=7Hz), 1.30(3H,d,J=7Hz), 1.45-1.95(3H,m), 2.55-3.08(4H,m), 3.12-4.35(10H,m)

Example 20

(1) (1R,5S,6S)-2-[(2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-{2-(4-(2-methoxyethyl)piperazinyl)carbonylmethylcarbamoylethylmercaptomethyl}pyrrolidin-4-yl]-thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

IR(Neat)cm^{-1} : 1765-1755, 1700, 1685, 1516, 1392
NMR($CDCl_3$) δ : 1.27(3H,d,J=7Hz), 1.34(3H,d,J=7Hz), 2.76(4H,m), 3.30(3H,s), 5.21(2H,s), 7.50-7.69(4H,m), 8.28(4H,d,J=9Hz)

(2) (1R,5S,6S)-2-[(2S,4S)-2-{2-(4-(2-methoxyethyl)piperazinyl)carbonylmethylcarbamoylethylmercaptomethyl}pyrrolidin-4-yl]-thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

UV $\lambda_{max}^{H_2O}$: 298nm
IR(Nujol)cm^{-1} : 1745-1750, 1650, 1585, 1380
NMR(D_2O) δ : 1.19(3H,d,J=7Hz), 1.27(3H,d,J=6Hz), 2.72(3H,s), 2.79-3.14(4H,m), 3.30(3H,s), 4.05-4.20(4H,m)

Example 21

(1) (1R,5S,6S)-2-[(2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-{2-(4-(2-carbamoyloxyethyl)piperazinylcarbonyl)methylcarbamoylethylmercaptomethyl}pyrrolidin-4-yl]-thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

IR(Neat)cm^{-1} : 1785, 1740, 1705, 1525, 1348
NMR($CDCl_3$) δ : 1.35(3H,d,J=6Hz), 1.48(3H,d,J=7Hz), 1.95-2.05(2H,m), 2.65-3.40(3H,m), 5.22(2H,s), 7.5-7.8(4H,dd,J=19Hz), 8.20(4H,d,J=8Hz)

(2) (1R,5S,6S)-2-[(2S,4S)-2-{2-(4-(2-carbamoyloxyethyl)piperazinylcarbonyl)methylcarbamoylethylmercaptomethyl}pyrrolidin-4-yl]-thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

$UV_{max}^{H_2O}$: 297.8nm
IR(Nujol)cm^{-1} : 1750, 1725-1710, 1600-1580
NMR(D_2O) δ : 1.22(3H,d,J=7Hz), 1.28(3H,d,J=6Hz), 1.6-1.9(4H,m), 2.5-2.9(1H,m)

Example 22

(1) (1R,5S,6S)-2-[(2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-{2-(4-(2-ureidoethyl)piperazinyl)carbonylmethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]-thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

IR(Nujol)cm^{-1} : 1770, 1700, 1610, 1525, 1350
NMR($CDCl_3$) δ : 1.27(3H,d,J=7Hz), 1.32(3H,d,J=6Hz), 2.85-3.90(11H,m), 4.80(2H,br. s), 5.25(2H,s), 5.37(2H,dd,J=18Hz), 7.56-7.68(4H,dd,J=18Hz), 8.26(4H,d,J=8Hz)

(2) (1R,5S,6S)-2-[(2S,4S)-2-{2-(4-(2-ureidoethyl)piperazinyl)carbonylmethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]-thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

$UV_{max}^{H_2O}$: 298.5nm
IR(Nujol)cm^{-1} : 1755, 1700, 1650, 1580
NMR($CDCl_3$) δ : 1.25(3H,d,J=7Hz), 1.33(3H,d,J=6Hz), 1.42-2.03(2H,m), 2.53-4.50(45H,m)

Example 23

(1) (1R,5S,6S)-2-[(2S,4S)-1-(p-nitrobenzyloxycarbon-

yl)-2-{(2-methoxymethyloxymethylcarbamoylethyl)mercaptomethyl}pyrrolidin-4-yl]-thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

IR(Neat)cm^{-1} : 1765-1750, 1700, 1680
NMR($CDCl_3$) δ : 1.27(3H,d,J=7Hz), 1.34(3H,d,J=7Hz), 2.25-2.60(3H,m), 3.35(3H,s), 5.21(2H,s), 7.55-7.70(4H,m), 8.26(4H,d,J=9Hz)

(2) (1R,5S,6S)-2-[(2S,4S)-2-{(2-methoxymethyloxymethylcarbamoylethyl)mercaptomethyl}pyrrolidin-4-yl]-thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

$UV_{max}^{H_2O}$: 298.7nm
IR(Nujol)cm^{-1} : 1750-1745, 1700, 1655, 1580, 1350
NMR(D_2O) δ : 1.20(3H,d,J=7Hz), 1.26(3H,d,J=7Hz), 2.73(3H,s), 2.77-3.15(4H,m), 3.33(3H,s), 4.10-4.15(3H,m)

Example 24

(1) (1R,5S,6S)-2-[(2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-{(2-methylcarbamoyloxymethylcarbamoylethyl)mercaptomethyl}pyrrolidin-4-yl]-thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

IR(Neat)cm^{-1} : 3500-3400, 1765, 1720-1700, 1605
NMR($CDCl_3$) δ : 1.1-1.8(6H,m), 5.10-5.75(4H,m), 7.4-7.8(4H,m), 8.21(4H,d,J=8.5Hz)

(2) (1R,5S,6S)-2-[(2S,4S)-2-{(2-methylcarbamoyloxymethylcarbamoylethyl)mercaptomethyl}pyrrolidin-4-yl]-thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

$UV_{max}^{H_2O}$: 297.8nm

IR(Nujol)cm^{-1} : 1750, 1725-1705, 1580
NMR(D_2O) δ : 1.25(3H,d,J=7Hz), 1.28(3H,d,J=8Hz), 1.6-1.9(2H,m), 2.4-2.9(2H,m)

Example 25

(1) (1R,5S,6S)-2-[(2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-{(2-ureidoethylcarbamoylethyl)mercaptomethyl}pyrrolidin-4-yl]-thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

IR(Neat)cm^{-1} : 1770-1760, 1710-1705, 1610-1605, 1525
NMR($CDCl_3$) δ : 1.27(3H,d,J=7Hz), 1.33(3H,d,J=7Hz), 3.10-3.95(13H,m), 4.85(2H,br. s), 5.24(2H,s), 5.50(2H,d,J=7Hz), 7.56-7.68(4H,dd,J=18Hz), 8.26(4H,d,J=8Hz)

(2) (1R,5S,6S)-2-[(2S,4S)-2-{(2-ureidoethylcarbamoylethyl)mercaptomethyl}pyrrolidin-4-yl]-thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

$UV_{max}^{H_2O}$: 298.2nm
IR(Nujol)cm^{-1} : 1755, 1650, 1580
NMR(D_2O) δ : 1.20(3H,d,J=9Hz), 1.25(3H,d,J=6Hz), 1.45-2.10(4H,m), 2.53-4.35(14H,m)

Example 26

(1) (1R,5S,6S)-2-[(2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-{(2-(p-nitrobenzyloxycarbonyl)aminoethylcarbamoylethyl)mercaptomethyl}pyrrolidin-4-yl]-thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

IR(Neat)cm^{-1} : 1765-1750, 1710, 1665-1650, 1510
NMR($CDCl_3$) δ : 1.24(3H,d,J=7Hz), 1.36(3H,d,J=7Hz), 2.35-2.50(2H,m), 3.15-3.46(3H,m),

3.56-4.40(12H,m), 5.12-5.50(6H,m),
7.36-7.80(6H,m), 8.24(6H,d,J=8Hz)

(2) (1R,5S,6S)-2-[(2S,4S)-2-{(2-aminoethylcarbamoylethyl)mercaptomethyl}pyrrolidin-4-yl]-thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic aciD

$UV_{max}^{H_2O}$: 298.5nm
IR(Nujol)cm^{-1} : 1770, 1705, 1610, 1525, 1350
NMR(D_2O) δ : 1.25(3H,d,J=7Hz), 1.33(3H,d,J=6Hz),
1.43-2.15(4H,m), 2.55-4.25(14H,m)

Example 27

(1) (1R,5S,6S)-2-[(2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-{(2-methoxymethyloxyethylcarbamoylethyl)mercaptomethyl}pyrrolidin-4-yl]-thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

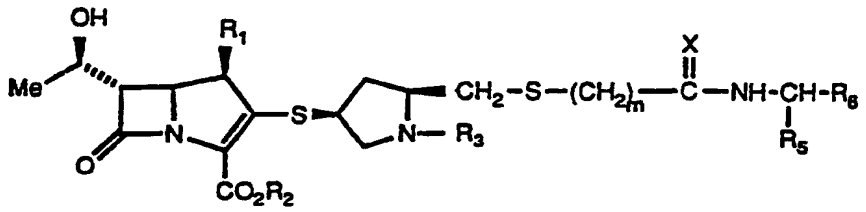
IR(Neat)cm^{-1} : 1770-1750, 1710-1700, 1690, 1605, 1520
NMR($CDCl_3$) δ : 1.28(3H,d,J=7Hz), 1.37(3H,d,J=7Hz),
1.65-2.10(5H,m), 2.35-2.85(4H,m),
2.94-3.10(4H,m), 3.25(3H,s),
5.40-5.74(2H,m), 7.56(2H,d,J=9Hz),
7.66(2H,d,J=9Hz), 8.26(4H,d,J=9Hz)

(2) (1R,5S,6S)-2-[(2S,4S)-2-{(2-methoxymethyloxyethylcarbamoylethyl)mercaptomethyl}pyrrolidin-4-yl]-thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

$UV_{max}^{H_2O}$: 299.0nm
IR(Nujol)cm^{-1} : 1760-1750, 1700, 1590-1580, 1380
NMR(D_2O) δ : 1.22(3H,d,J=7Hz), 1.28(3H,d,J=7Hz),
1.48-2.00(4H,m), 2.46-2.95(2H,m),
3.15(3H,s)

The specific examples of the compound of formula(I)

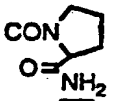
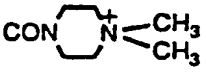
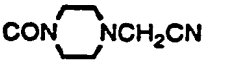
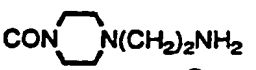
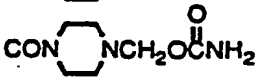
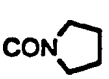
which can be prepared in the same manner as that of Example 1 are listed in the following Table.

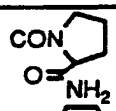
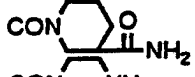
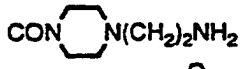
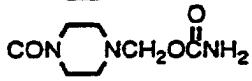
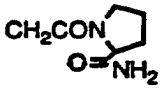
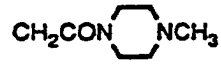
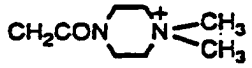


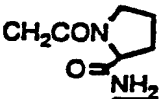
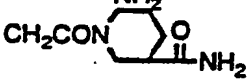
No	R_1	R_2	R_3	R_5	R_6	X	m
1	Me	H	H	H	CH	O	1
2	Me	H	H	H	CN	O	1
3	Me	H	H	H	NH_2	O	1
4	Me	H	H	H	$CONH_2$	O	1
5	Me	H	H	H	$CONHCH_3$	O	1
6	Me	H	H	H	$CON(CH_3)_2$	O	1
7	Me	H	H	H	$OCONH_2$	O	1
8	Me	H	H	H	$NHCONH_2$	O	1
9	Me	H	H	H	CH	O	2
10	Me	H	H	H	CN	O	2
11	Me	H	H	H	NH_2	O	2
12	Me	H	H	H	$CONH_2$	O	2
13	Me	H	H	H	$CONHCH_3$	O	2
14	Me	H	H	H	$CON(CH_3)_2$	O	2
15	Me	H	H	H	$OCONH_2$	O	2

No	R_1	R_2	R_3	R_5	R_6	X	m
16	Me	H	H	H	$NHCONH_2$	O	2
17	Me	H	H	H	CH_2OH	O	1
18	Me	H	H	H	CH_2CN	O	1
19	Me	H	H	H	CH_2NH_2	O	1
20	Me	H	H	H	$CH_2O\overset{O}{\overset{\|}{C}}NH_2$	O	1
21	Me	H	H	H	$CH_2\overset{O}{\overset{\|}{C}}NH_2$	O	1
22	Me	H	H	H	$CH_2\overset{O}{\overset{\|}{C}}NHCH_3$	O	1
23	Me	H	H	H	$CH_2\overset{O}{\overset{\|}{C}}N(CH_3)_2$	O	1
24	Me	H	H	H	$CH_2NHCONH_2$	O	1
25	Me	H	H	H	CH_2CN	O	2
26	Me	H	H	H	CH_2OH	O	2
27	Me	H	H	H	CH_2NH_2	O	2
28	Me	H	H	H	CH_2CONH_2	O	2
29	Me	H	H	H	$CH_2CONHCH_3$	O	2
30	Me	H	H	H	$CH_2CON(CH_3)_2$	O	2
31	Me	H	$-\overset{H}{\overset{\|}{C}}=NH$	H	CH_2OH	O	1
32	Me	H	$-\overset{H}{\overset{\|}{C}}=NH$	H	CH_2CN	O	1
33	Me	H	$-\overset{H}{\overset{\|}{C}}=NH$	H	CH_2NH_2	O	1
34	Me	H	$-\overset{H}{\overset{\|}{C}}=NH$	H	CH_2CONH_2	O	1

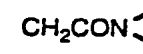
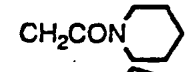
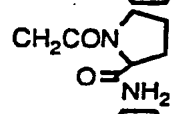
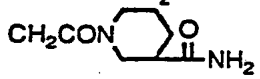
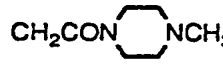
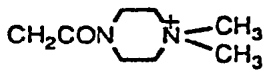
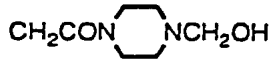
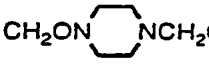
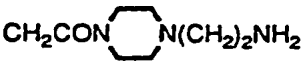
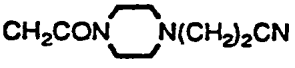
No	R_1	R_2	R_3	R_5	R_6	X	m
35	Me	H	$-\underset{H}{C}=NH$	H	CH_2OCONH_2	O	1
36	Me	H	$-\underset{H}{C}=NH$	H	$CH_2NHCONH_2$	O	1
37	Me	H	$-\underset{H}{C}=NH$	H	CH_2OH	O	2
38	Me	H	$-\underset{H}{C}=NH$	H	CH_2CN	O	2
39	Me	H	$-\underset{H}{C}=NH$	H	CH_2NH_2	O	2
40	Me	H	$-\underset{H}{C}=NH$	H	CH_2COH_2	O	2
41	Me	H	$-\underset{H}{C}=NH$	H	CH_2OCONH_2	O	2
42	Me	H	$-\underset{H}{C}=NH$	H	$CH_2NH_2CONH_2$	O	2
43	Me	H	$-\underset{CH_3}{C}=NH$	H	CH_2OH	O	1
44	Me	H	$-\underset{CH_3}{C}=NH$	H	CH_2CN	O	1
45	Me	H	$-\underset{CH_3}{C}=NH$	H	CH_2NH_2	O	1
46	Me	H	$-\underset{CH_3}{C}=NH$	H	CH_2CONH_2	O	1
47	Me	H	$-\underset{CH_3}{C}=NH$	H	CH_2OCONH_2	O	1
48	Me	H	$-\underset{CH_3}{C}=NH$	H	$CH_2NHCONH_2$	O	1
49	Me	H	$-\underset{CH_3}{C}=NH$	H	CH_2OH	O	2
50	Me	H	$-\underset{CH_3}{C}=NH$	H	CH_2CN	O	2
51	Me	H	$-\underset{CH_3}{C}=NH$	H	CH_2NH_2	O	2
52	Me	H	$-\underset{CH_3}{C}=NH$	H	CH_2CONH_2	O	2
53	Me	H	$-\underset{CH_3}{C}=NH$	H	CH_2OCONH_2	O	2

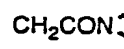
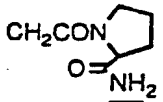
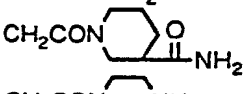
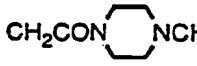
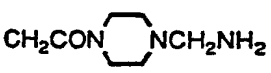
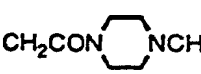
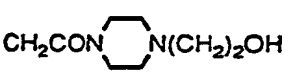
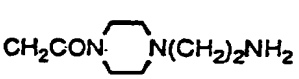
No	R_1	R_2	R_3	R_5	R_6	X	m
54	Me	H	$-C(=NH)-CH_3$	H	$CH_2CONHCH_3$	O	2
55	Me	H	$-C(=NH)-CH_3$	H	$CH_2NHCONH_2$	O	2
56	Me	H	H	H		O	1
57	Me	H	H	H		O	1
58	Me	H	H	H		O	1
59	Me	H	H	H		O	1
60	Me	H	H	H		O	1
61	Me	H	H	H		O	1
62	Me	H	H	H		O	1
63	Me	H	H	H		O	1
64	Me	anion	H	H		O	1
65	Me	H	H	H		O	1
66	Me	H	H	H		O	1
67	Me	H	H	H		O	1
68	Me	H	H	H		O	1
69	Me	H	H	H		O	2
70	Me	H	H	H		O	2
71	Me	H	H	H		O	2
72	Me	H	H	H		O	2

No	R_1	R_2	R_3	R_5	R_6	X	m
73	Me	H	H	H		O	2
74	Me	H	H	H		O	2
75	Me	H	H	H		O	2
76	Me	H	H	H		O	2
77	Me	anion	H	H		O	2
78	Me	H	H	H		O	2
79	Me	H	H	H		O	2
80	Me	H	H	H		O	2
81	Me	H	H	H		O	2
82	Me	H	H	H		O	1
83	Me	H	H	H		O	1
84	Me	H	H	H		O	1
85	Me	H	H	H		O	1
86	Me	H	H	H		O	1
87	Me	H	H	H		O	1
88	Me	H	H	H		O	1
89	Me	H	H	H		O	1
90	Me	anion	H	H		O	1
91	Me	H	H	H		O	1

No	R_1	R_2	R_3	R_5	R_6	X	m
92	Me	H	H	H		O	1
93	Me	H	H	H		O	1
94	Me	H	H	H		O	1
95	Me	H	H	H		O	2
96	Me	H	H	H		O	2
97	Me	H	H	H		O	2
98	Me	H	H	H		O	2
99	Me	H	H	H		O	2
100	Me	H	H	H		O	2
101	Me	H	H	H		O	2
102	Me	H	H	H		O	2
103	Me	H	H	H		O	2
104	Me	H	H	H		O	2
105	Me	H	H	H		O	2
106	Me	H	H	H		O	2
107	Me	H		H	CN	O	1
108	Me	H		H	CN	O	2
109	Me	H		H	CH_2CN	O	1
110	Me	H		H	$(CH_2)_2CN$	O	2

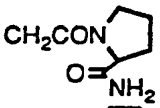
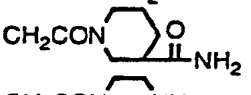
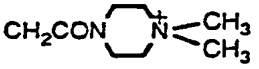
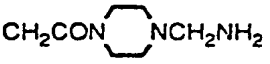
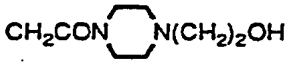
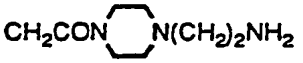
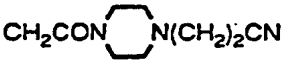
No	R_1	R_2	R_3	R_5	R_6	X	m
111	Me	H	$-\overset{H}{\underset{\vert}{C}}=NH$	H	$(CH_2)_2OH$	O	1
112	Me	H	$-\overset{H}{\underset{\vert}{C}}=NH$	H	$(CH_2)_2OH$	O	2
113	Me	H	$-\overset{H}{\underset{\vert}{C}}=NH$	H	$(CH_2)_2\overset{O}{\overset{\Vert}{C}}NH_2$	O	1
114	Me	H	$-\overset{H}{\underset{\vert}{C}}=NH$	H	$(CH_2)_2\overset{O}{\overset{\Vert}{C}}NH_2$	O	2
115	Me	H	$-\overset{CH_3}{\underset{\vert}{C}}=NH$	H	CN	O	1
116	Me	H	$-\overset{CH_3}{\underset{\vert}{C}}=NH$	H	CN	O	2
117	Me	H	$-\overset{CH_3}{\underset{\vert}{C}}=NH$	H	$(CH_2)_2CN$	O	1
118	Me	H	$-\overset{CH_3}{\underset{\vert}{C}}=NH$	H	$(CH_2)_2OH$	O	2
119	Me	H	$-\overset{CH_3}{\underset{\vert}{C}}=NH$	H	$(CH_2)_2OH$	O	1
120	Me	H	$-\overset{CH_3}{\underset{\vert}{C}}=NH$	H	$(CH_2)_2OH$	O	2
121	Me	H	$-\overset{CH_3}{\underset{\vert}{C}}=NH$	H	$(CH_2)_2NH_2$	O	1
122	Me	H	$-\overset{CH_3}{\underset{\vert}{C}}=NH$	H	$(CH_2)_2NH_2$	O	2
123	Me	H	$-\overset{CH_3}{\underset{\vert}{C}}=NH$	H	$(CH_2)_2CONH_2$	O	1
124	Me	H	$-\overset{CH_3}{\underset{\vert}{C}}=NH$	H	$(CH_2)_2CONH_2$	O	2
125	Me	H	H	CH	CH_2OH	O	1
126	Me	H	H	CH	CH_2CN	O	1
127	Me	H	H	CH	CH_2NH_2	O	1
128	Me	H	H	CH	CH_2OCONH_2	O	1
129	Me	H	H	CH	CH_2CONH_2	O	1

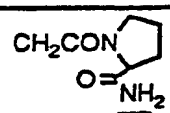
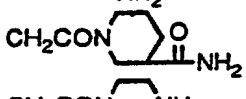
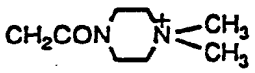
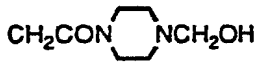
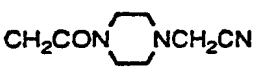
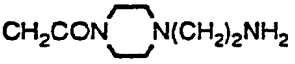
No	R_1	R_2	R_3	R_5	R_6	X	m
130	Me	H	H	CH	$CH_2NHCONH_2$	O	1
131	Me	H	H	CH		O	1
132	Me	H	H	CH		O	1
133	Me	H	H	CH		O	1
134	Me	H	H	CH		O	1
135	Me	H	H	CH		O	1
136	Me	H	H	CH		O	1
137	Me	H	H	CH		O	1
138	Me	H	H	CH		O	1
139	Me	anion	H	CH		O	1
140	Me	H	H	CH		O	1
141	Me	H	H	CH		O	1
142	Me	H	H	CH		O	1
143	Me	H	H	CH		O	1
144	Me	H	H	CH		O	1
145	Me	H	H	CH		O	1
146	Me	H	H	CH	CH_2OH	O	2
147	Me	H	H	CH	CH_2CN	O	2
148	Me	H	H	CH	CH_2NH_2	O	2

No	R_1	R_2	R_3	R_5	R_6	X	m
149	Me	H	H	CH	CH_2CONH_2	O	2
150	Me	H	H	CH	$CH_2CONHCH_3$	O	2
151	Me	H	H	CH	$CH_2CON(CH_3)_2$	O	2
152	Me	H	H	CH	CH_2OCONH_2	O	2
153	Me	H	H	CH	$CH_2NHCONH_2$	O	2
154	Me	H	H	CH		O	2
155	Me	H	H	CH		O	2
156	Me	H	H	CH		O	2
157	Me	H	H	CH		O	2
158	Me	H	H	CH		O	2
159	Me	H	H	CH		O	2
160	Me	H	H	CH		O	2
161	Me	H	H	CH		O	2
162	Me	anion	H	CH		O	2
163	Me	H	H	CH		O	2
164	Me	H	H	CH		O	2
165	Me	H	H	CH		O	2
166	Me	H	H	CH		O	2
167	Me	H	H	CH		O	2

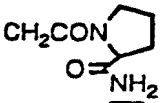
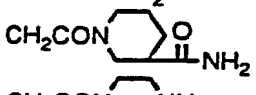
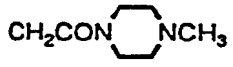
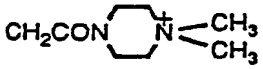
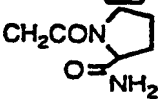
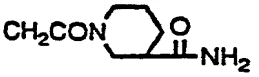
No	R_1	R_2	R_3	R_5	R_6	X	m
168	Me	H	H	CH	CH_2CON ⟨piperazine⟩ $N(CH_2)_2CN$	O	2
169	Me	H	$-\overset{\overset{H}{\vert}}{C}=NH$	CH	CH_2OH	O	1
170	Me	H	$-\overset{\overset{H}{\vert}}{C}=NH$	CH	CH_2CN	O	1
171	Me	H	$-\overset{\overset{H}{\vert}}{C}=NH$	CH	CH_2NH_2	O	1
172	Me	H	$-\overset{\overset{H}{\vert}}{C}=NH$	CH	CH_2CONH_2	O	1
173	Me	H	$-\overset{\overset{H}{\vert}}{C}=NH$	CH	CH_2OH	O	2
174	Me	H	$-\overset{\overset{H}{\vert}}{C}=NH$	CH	CH_2CN	O	2
175	Me	H	$-\overset{\overset{H}{\vert}}{C}=NH$	CH	CH_2NH_2	O	2
176	Me	H	$-\overset{\overset{H}{\vert}}{C}=NH$	CH	CH_2CONH_2	O	2
177	Me	H	$-\overset{\overset{H}{\vert}}{C}=NH$	CH	$CH_2O\overset{\overset{O}{\Vert}}{C}NH_2$	O	2
178	Me	H	$-\overset{\overset{CH_3}{\vert}}{C}=NH$	CH	CH_2OH	O	1
179	Me	H	$-\overset{\overset{CH_3}{\vert}}{C}=NH$	CH	CH_2CN	O	1
180	Me	H	$-\overset{\overset{CH_3}{\vert}}{C}=NH$	CH	CH_2NH_2	O	1
181	Me	H	$-\overset{\overset{CH_3}{\vert}}{C}=NH$	CH	CH_2CONH_2	O	1
182	Me	H	$-\overset{\overset{CH_3}{\vert}}{C}=NH$	CH	$CH_2O\overset{\overset{O}{\Vert}}{C}NH_2$	O	1
183	Me	H	$-\overset{\overset{CH_3}{\vert}}{C}=NH$	CH	$CH_2NH_2CONH_2$	O	1
184	Me	H	$-\overset{\overset{CH_3}{\vert}}{C}=NH$	CH	CH_2OH	O	2
185	Me	H	$-\overset{\overset{CH_3}{\vert}}{C}=NH$	CH	CH_2CN	O	2
186	Me	H	$-\overset{\overset{CH_3}{\vert}}{C}=NH$	CH	CH_2NH_2	O	2

No	R_1	R_2	R_3	R_5	R_6	X	m
187	Me	H	$-\overset{CH_3}{\underset{}{C}}=NH$	CH	CH_2CONH_2	O	2
188	Me	H	$-\overset{CH_3}{\underset{}{C}}=NH$	CH	CH_2OCONH_2	O	2
189	Me	H	$-\overset{CH_3}{\underset{}{C}}=NH$	CH	$CH_2NHCONH_2$	O	2
190	Me	H	H	CN	CH_2OH	O	1
191	Me	H	H	CN	CH_2CN	O	1
192	Me	H	H	CN	CH_2NH_2	O	1
193	Me	H	H	CN	CH_2CONH_2	O	1
194	Me	H	H	CN	$CH_2CONHCH_3$	O	1
195	Me	H	H	CN	$CH_2CON(CH_3)_2$	O	1
196	Me	H	H	CN	CH_2OCONH_2	O	1
197	Me	H	H	CN	$CH_2NHCONH_2$	O	1
198	Me	H	H	CN	CH_2OH	O	2
199	Me	H	H	CN	CH_2CN	O	2
200	Me	H	H	CN	CH_2NH_2	O	2
201	Me	H	H	CN	CH_2CONH_2	O	2
202	Me	H	H	CN	$CH_2CON(CH_3)_2$	O	2
203	Me	H	H	CN	$CH_2CON(CH_3)_2$	O	2
204	Me	H	H	CN	$CH_2NHCONH_2$	O	2
205	Me	H	H	CN	CH_2OCONH_2	O	2

No	R_1	R_2	R_3	R_5	R_6	X	m
206	Me	H	H	CN		0	1
207	Me	H	H	CN		0	1
208	Me	H	H	CN		0	1
209	Me	H	H	CN		0	1
210	Me	H	H	CN		0	1
211	Me	H	H	CN		0	1
212	Me	H	H	CN		0	1
213	Me	H	H	CN		0	1
214	Me	anion	H	CN		0	1
215	Me	H	H	CN		0	1
216	Me	H	H	CN		0	1
217	Me	H	H	CN		0	1
218	Me	H	H	CN		0	1
219	Me	H	H	CN		0	1
220	Me	H	H	CN		0	1
221	Me	H	H	CN		0	2
222	Me	H	H	CN		0	2
223	Me	H	H	CN		0	2
224	Me	H	H	CN		0	2

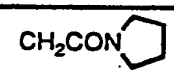
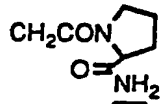
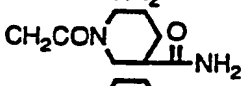
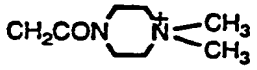
No	R_1	R_2	R_3	R_5	R_6	X	m
225	Me	H	H	CN		O	2
226	Me	H	H	CN		O	2
227	Me	H	H	CN		O	2
228	Me	H	H	CN		O	2
229	Me	anion	H	CN		O	2
230	Me	H	H	CN		O	2
231	Me	H	H	CN		O	2
232	Me	H	H	CN		O	2
233	Me	H	H	CN		O	2
234	Me	H	H	CN		O	2
235	Me	H	H	CN		O	2
236	Me	H	H	CH_2OH	CH_2OH	O	1
237	Me	H	H	CH_2OH	CH_2CN	O	1
238	Me	H	H	CH_2OH	CH_2NH_2	O	1
239	Me	H	H	CH_2OH	CH_2OCONH_2	O	1
240	Me	H	H	CH_2OH	$CH_2NHCONH_2$	O	1
241	Me	H	H	CH_2OH	CH_2CONH_2	O	1
242	Me	H	H	CH_2OH	$CH_2CONHCH_3$	O	1
243	Me	H	H	CH_2OH	$CH_2CON(CH_3)_2$	O	1

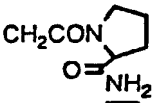
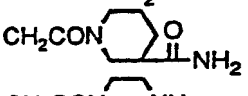
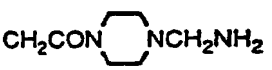
No	R_1	R_2	R_3	R_5	R_6	X	m
244	Me	H	H	CH_2OH	CH_2OH	O	2
245	Me	H	H	CH_2OH	CH_2CN	O	2
246	Me	H	H	CH_2OH	CH_2NH_2	O	2
247	Me	H	H	CH_2OH	CH_2OCONH_2	O	2
248	Me	H	H	CH_2OH	$CH_2NHCONH_2$	O	2
249	Me	H	H	CH_2OH	CH_2CONH_2	O	2
250	Me	H	H	CH_2OH	$CH_2CONHCH_3$	O	2
251	Me	H	H	CH_2OH	$CH_2CON(CH_3)_2$	O	2
252	Me	H	H	CH_2OH	CH_2CH_2OH	O	1
253	Me	H	H	CH_2OH	CH_2CH_2CN	O	1
254	Me	H	H	CH_2OH	$CH_2CH_2NH_2$	O	1
255	Me	H	H	CH_2OH	$CH_2CH_2CONH_2$	O	1
256	Me	H	H	CH_2OH	$CH_2CH_2NHCONH_2$	O	1
257	Me	H	H	CH_2OH	$CH_2CH_2OCONH_2$	O	1
258	Me	H	H	CH_2OH	CH_2CH_2OH	O	2
259	Me	H	H	CH_2OH	CH_2CH_2CN	O	2
260	Me	H	H	CH_2OH	$CH_2CH_2NH_2$	O	2
261	Me	H	H	CH_2OH	$CH_2CH_2OCONH_2$	O	2
262	Me	H	H	CH_2OH	$CH_2CH_2CONH_2$	O	2

No	R_1	R_2	R_3	R_5	R_6	X	m
263	Me	H	H	CH_2OH	$CH_2CH_2NHCONH_2$	O	1
264	Me	H	H	CH_2OH		O	1
265	Me	H	H	CH_2OH		O	1
266	Me	H	H	CH_2OH		O	1
267	Me	H	H	CH_2OH		O	1
268	Me	H	H	CH_2OH		O	1
269	Me	H	H	CH_2OH		O	1
270	Me	H	H	CH_2OH		O	1
271	Me	H	H	CH_2OH		O	1
272	Me	anion	H	CH_2OH		O	1
273	Me	H	H	CH_2OH		O	1
274	Me	H	H	CH_2OH		O	1
275	Me	H	H	CH_2OH		O	1
276	Me	H	H	CH_2OH		O	2
277	Me	H	H	CH_2OH		O	2
278	Me	H	H	CH_2OH		O	2
279	Me	H	H	CH_2OH		O	2
280	Me	H	H	CH_2OH		O	2
281	Me	H	H	CH_2OH		O	2

No	R_1	R_2	R_3	R_5	R_6	X	m
282	Me	H	H	CH_2OH	CH_2CON⟨⟩NH	O	2
283	Me	H	H	CH_2OH	CH_2CON⟨⟩NCH_3	O	2
284	Me	anion	H	CH_2OH	CH_2CON⟨⟩$N^+(CH_3)_2$	O	2
285	Me	H	H	CH_2OH	CH_2CON⟨⟩NCH_2OH	O	2
286	Me	H	H	CH_2OH	CH_2CON⟨⟩NCH_2NH_2	O	2
287	Me	H	H	CH_2OH	CH_2CON⟨⟩NCH_2CN	O	2
288	Me	H	$-\underset{H}{C}=NH$	CH_2OH	CH_2OH	O	1
289	Me	H	$-\underset{H}{C}=NH$	CH_2OH	CH_2CN	O	1
290	Me	H	$-\underset{H}{C}=NH$	CH_2OH	CH_2NH_2	O	1
291	Me	H	$-\underset{H}{C}=NH$	CH_2OH	CH_2OCONH_2	O	1
292	Me	H	$-\underset{H}{C}=NH$	CH_2OH	CH_2CONH_2	O	1
293	Me	H	$-\underset{H}{C}=NH$	CH_2OH	$CH_2NHCONH_2$	O	1
294	Me	H	$-\underset{H}{C}=NH$	CH_2OH	CH_2OH	O	2
295	Me	H	$-\underset{H}{C}=NH$	CH_2OH	CH_2CN	O	2
296	Me	H	$-\underset{H}{C}=NH$	CH_2OH	CH_2NH_2	O	2
297	Me	H	$-\underset{H}{C}=NH$	CH_2OH	CH_2OCONH_2	O	2
298	Me	H	$-\underset{H}{C}=NH$	CH_2OH	$CH_2NHCONH_2$	O	2
299	Me	H	$-\underset{H}{C}=NH$	CH_2OH	CH_2CONH_2	O	2
300	Me	H	$-\underset{CH_3}{C}=NH$	CH_2OH	CH_2OH	O	1

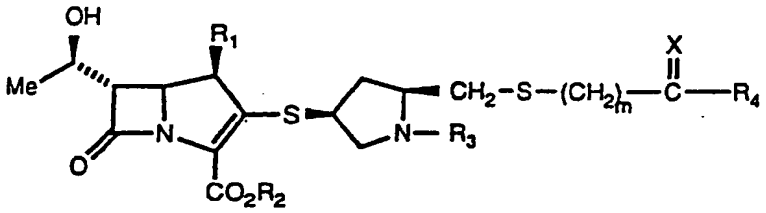
No	R_1	R_2	R_3	R_5	R_6	X	m
301	Me	H	$-\overset{CH_3}{\underset{}{C}}=NH$	CH_2OH	CH_2CN	O	1
302	Me	H	$-\overset{CH_3}{\underset{}{C}}=NH$	CH_2OH	CH_2NH_2	O	1
303	Me	H	$-\overset{CH_3}{\underset{}{C}}=NH$	CH_2OH	CH_2OCONH_2	O	1
304	Me	H	$-\overset{CH_3}{\underset{}{C}}=NH$	CH_2OH	CH_2CONH_2	O	1
305	Me	H	$-\overset{CH_3}{\underset{}{C}}=NH$	CH_2OH	$CH_2NHCONH_2$	O	1
306	Me	H	$-\overset{CH_3}{\underset{}{C}}=NH$	CH_2OH	CH_2OH	O	2
307	Me	H	$-\overset{CH_3}{\underset{}{C}}=NH$	CH_2OH	CH_2CN	O	2
308	Me	H	$-\overset{CH_3}{\underset{}{C}}=NH$	CH_2OH	CH_2NH_2	O	2
309	Me	H	$-\overset{CH_3}{\underset{}{C}}=NH$	CH_2OH	CH_2OCONH_2	O	2
310	Me	H	$-\overset{CH_3}{\underset{}{C}}=NH$	CH_2OH	CH_2CONH_2	O	2
311	Me	H	$-\overset{CH_3}{\underset{}{C}}=NH$	CH_2OH	$CH_2NHCONH_2$	O	2
312	Me	H	H	CH_2CONH_2	CH_2OH	O	1
313	Me	H	H	CH_2CONH_2	CH_2CN	O	1
314	Me	H	H	CH_2CCNH_2	CH_2NH_2	O	1
315	Me	H	H	CH_2CONH_2	CH_2CONH_2	O	1
316	Me	H	H	CH_2CONH_2	$CH_2NHCONH_2$	O	1
317	Me	H	H	CH_2CONH_2	CH_2OCONH_2	O	1
318	Me	H	H	CH_2CONH_2	CH_2CON 	O	1
319	Me	H	H	CH_2CONH_2	CH_2CON 	O	1

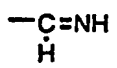
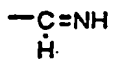
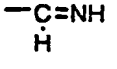
No	R_1	R_2	R_3	R_5	R_6	X	m
320	Me	H	H	CH_2CONH_2		O	1
321	Me	H	H	CH_2CONH_2		O	1
322	Me	H	H	CH_2CONH_2		O	1
323	Me	H	H	CH_2CONH_2		O	1
324	Me	H	H	CH_2CONH_2		O	1
325	Me	H	H	CH_2CONH_2		O	1
326	Me	anion	H	CH_2CONH_2		O	1
327	Me	H	H	CH_2CONH_2		O	1
328	Me	H	H	CH_2CONH_2		O	1
329	Me	H	H	CH_2CONH_2		O	1
330	Me	H	H	CH_2CONH_2	CH_2CH_2OH	O	1
331	Me	H	H	CH_2CONH_2	CH_2CH_2CN	O	1
332	Me	H	H	CH_2CONH_2	$CH_2CH_2NH_2$	O	1
333	Me	H	H	CH_2CONH_2	$CH_2CH_2CONH_2$	O	1
334	Me	H	H	CH_2CONH_2	$CH_2CH_2OCONH_2$	O	1
335	Me	H	H	CH_2CONH_2	$CH_2CH_2NHCONH_2$	O	1
336	Me	H	H	CH_2CONH_2	CH_2OH	O	2
337	Me	H	H	CH_2CONH_2	CH_2CN	O	2
338	Me	H	H	CH_2CONH_2	CH_2NH_2	O	2

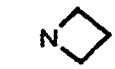
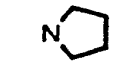
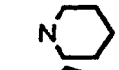
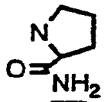
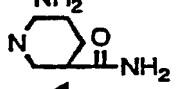
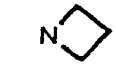
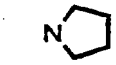
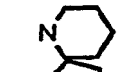
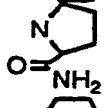
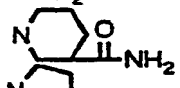
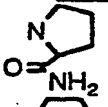
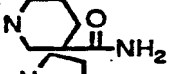
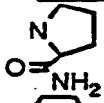
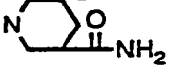
No	R_1	R_2	R_3	R_5	R_6	X	m
339	Me	H	H	CH_2CONH_2	CH_2OCONH_2	O	2
340	Me	H	H	CH_2CONH_2	CH_2CONH_2	O	2
341	Me	H	H	CH_2CONH_2	$CH_2NHCONH_2$	O	2
342	Me	H	H	CH_2CONH_2		O	2
343	Me	H	H	CH_2CONH_2		O	2
344	Me	H	H	CH_2CONH_2		O	2
345	Me	H	H	CH_2CONH_2		O	2
346	Me	H	H	CH_2CONH_2		O	2
347	Me	H	H	CH_2CONH_2		O	2
348	Me	H	H	CH_2CONH_2		O	2
349	Me	H	H	CH_2CONH_2		O	2
350	Me	anion	H	CH_2CONH_2		O	2
351	Me	H	H	CH_2CONH_2		O	2
352	Me	H	H	CH_2CONH_2		O	2
353	Me	H	H	CH_2CONH_2		O	2
354	Me	H	H	CH_2CONH_2	CH_2CH_2OH	O	2
355	Me	H	H	CH_2CONH_2	CH_2CH_2CN	O	2
356	Me	H	H	CH_2CONH_2	$CH_2CH_2NH_2$	O	2
357	Me	H	H	CH_2CONH_2	$CH_2CH_2OCONH_2$	O	2

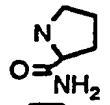
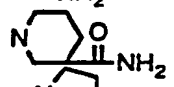
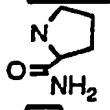
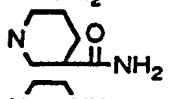
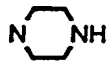
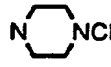
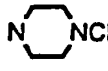
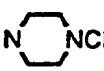
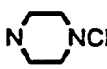
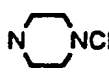
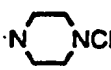
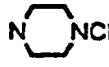
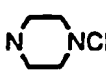
No	R_1	R_2	R_3	R_5	R_6	X	m
358	Me	H	H	CH_2CONH_2	$CH_2CH_2NHCONH_2$	O	2
359	Me	H	H	CH_2CONH_2	$CH_2CH_2CONH_2$	O	2
360	Me	H	H	CH_2CONH_2	$CH_2CH_2CONHCH_3$	O	2
361	Me	H	H	CH_2CONH_2	$CH_2CH_2CON(CH_3)_2$	O	2
362	Me	H	$-\underset{H}{C}=NH$	CH_2CONH_2	CH_2OH	O	1
363	Me	H	$-\underset{H}{C}=NH$	CH_2CONH_2	CH_2NH_2	O	1
364	Me	H	$-\underset{H}{C}=NH$	CH_2CONH_2	CH_2CN	O	1
365	Me	H	$-\underset{H}{C}=NH$	CH_2CONH_2	CH_2OCONH_2	O	1
366	Me	H	$-\underset{H}{C}=NH$	CH_2CONH_2	CH_2CONH_2	O	1
367	Me	H	$-\underset{H}{C}=NH$	CH_2CONH_2	$CH_2NHCONH_2$	O	1
368	Me	H	$-\underset{H}{C}=NH$	CH_2CONH_2	CH_2OH	O	2
369	Me	H	$-\underset{H}{C}=NH$	CH_2CONH_2	CH_2NH_2	O	2
370	Me	H	$-\underset{H}{C}=NH$	CH_2CONH_2	CH_2CN	O	2
371	Me	H	$-\underset{H}{C}=NH$	CH_2CONH_2	CH_2CONH_2	O	2
372	Me	H	$-\underset{H}{C}=NH$	CH_2CONH_2	$CH_2NHCONH_2$	O	2
373	Me	H	$-\underset{CH_3}{C}=NH$	CH_2CONH_2	CH_2OH	O	1
374	Me	H	$-\underset{CH_3}{C}=NH$	CH_2CONH_2	CH_2CN	O	1
375	Me	H	$-\underset{CH_3}{C}=NH$	CH_2CONH_2	CH_2NH_2	O	1
376	Me	H	$-\underset{CH_3}{C}=NH$	CH_2CONH_2	CH_2OCONH_2	O	1

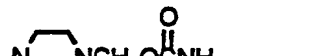
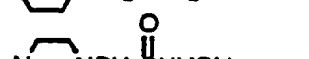
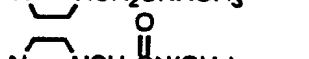
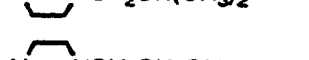
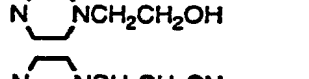
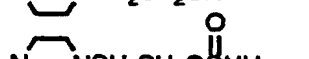
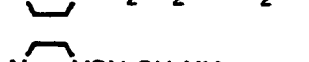
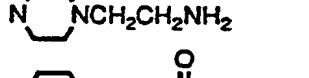
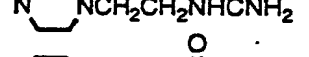
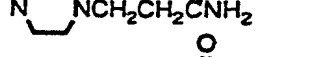
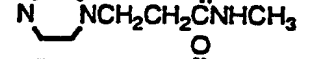
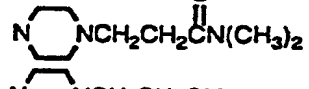
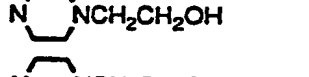
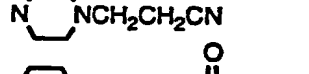
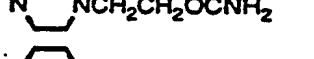
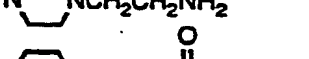
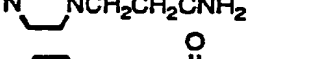
No	R_1	R_2	R_3	R_5	R_6	X	m
377	Me	H	$-\overset{\overset{CH_3}{\vert}}{C}=NH$	CH_2CONH_2	$CH_2CH_2NHCONH_2$	O	1
378	Me	H	$-\overset{\overset{CH_3}{\vert}}{C}=NH$	CH_2CONH_2	$CH_2CH_2CONH_2$	O	1
379	Me	H	$-\overset{\overset{CH_3}{\vert}}{C}=NH$	CH_2CONH_2	$CH_2CH_2CONHCH_3$	O	2
280	Me	H	$-\overset{\overset{CH_3}{\vert}}{C}=NH$	CH_2CONH_2	$CH_2CH_2CON(CH_3)_2$	O	2
381	Me	H	$-\overset{\overset{CH_3}{\vert}}{C}=NH$	CH_2CONH_2	CH_2OH	O	2
382	Me	H	$-\overset{\overset{CH_3}{\vert}}{C}=NH$	CH_2CONH_2	CH_2NH_2	O	2
383	Me	H	$-\overset{\overset{CH_3}{\vert}}{C}=NH$	CH_2CONH_2	CH_2CN	O	2
384	Me	H	$-\overset{\overset{CH_3}{\vert}}{C}=NH$	CH_2CONH_2	CH_2OCONH_2	O	2
385	Me	H	$-\overset{\overset{CH_3}{\vert}}{C}=NH$	CH_2CONH_2	CH_2CONH_2	O	2

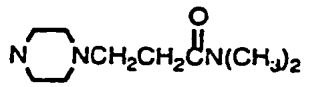
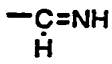
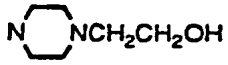
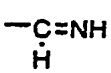
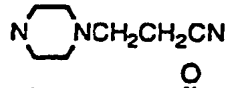
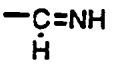
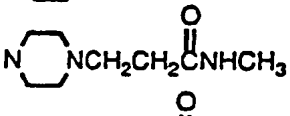
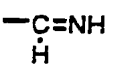
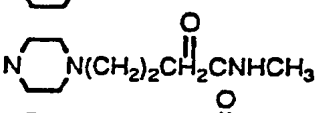
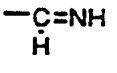
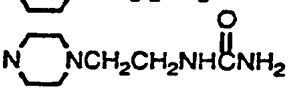
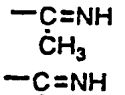
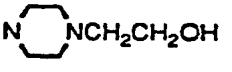
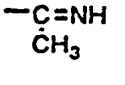
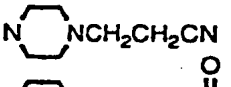
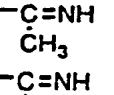
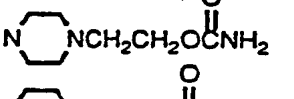
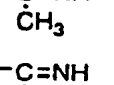
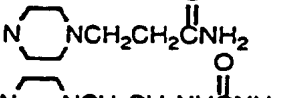
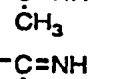
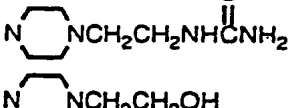
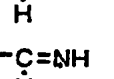
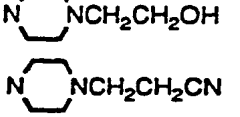
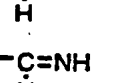
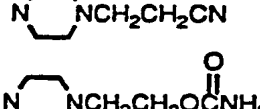
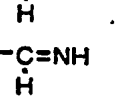
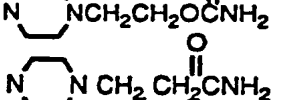
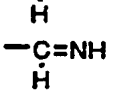
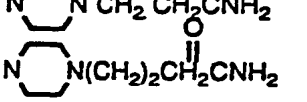
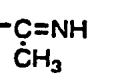
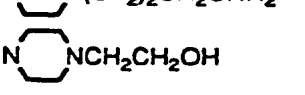
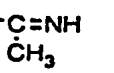
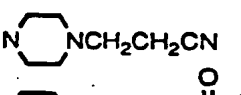
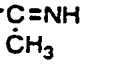
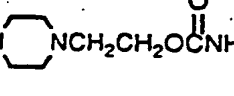


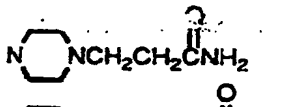
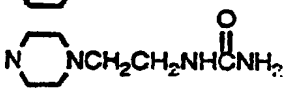
No	R_1	R_2	R_3	R_4	X	m
386	Me	H	H	$NHCH_3$	O	1
387	Me	H	H	NH_2	O	2
388	Me	H	H	$NHCH_3$	O	2
389	Me	H	H	$N(CH_3)_2$	O	1
390	Me	H	H	MeNEt	O	1
391	Me	H	H	MeNiPr	O	1
392	Me	H	H	EtNiPr	O	1
393	Me	H	H	$N(iPr)_2$	O	1
394	Me	H	H	MeNEt	O	2
395	Me	H	H	$N(Et)_2$	O	2
396	Me	H	H	EtNiPr	O	2
397	Me	H	H	$N(iPr)_2$	O	2
398	Me	H		$N(iPr)_2$	O	1
399	Me	H		$NHCH_3$	O	2
400	Me	H		NH_2	O	2

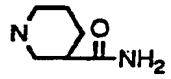
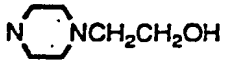
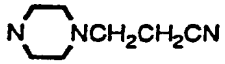
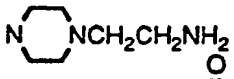
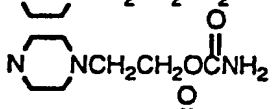
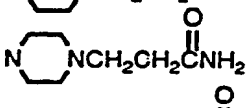
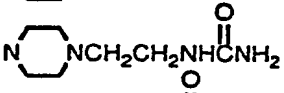
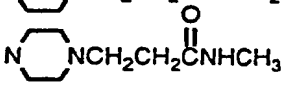
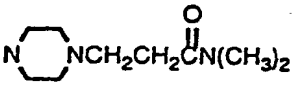
No	R_1	R_2	R_3	R_4	X	m
401	Me	H	$-C(=NH)CH_3$	$NHCH_3$	O	1
402	Me	H	$-C(=NH)CH_3$	NH_2	O	2
403	Me	H	$-C(=NH)CH_3$	$NHCH_3$	O	2
404	Me	H	H		O	1
405	Me	H	H		O	1
406	Me	H	H		O	1
407	Me	H	H		O	1
408	Me	H	H		O	1
409	Me	H	H		O	1
410	Me	H	H		O	2
411	Me	H	H		O	2
412	Me	H	H		O	2
413	Me	H	H		O	2
414	Me	H	H		O	2
415	Me	H	H		O	2
416	Me	H	$-C(=NH)H$		O	1
417	Me	H	$-C(=NH)H$		O	1
418	Me	H	$-C(=NH)H$		O	2
419	Me	H	$-C(=NH)H$		O	2

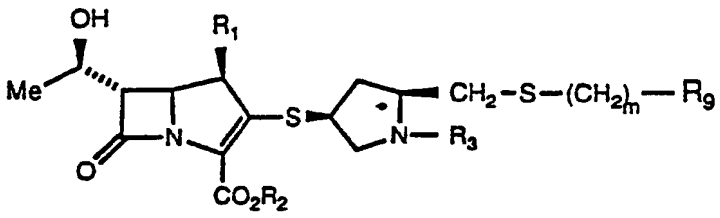
No	R_1	R_2	R_3	R_4	X	m
420	Me	H	$-C(=NH)CH_3$		O	1
421	Me	H	$-C(=NH)CH_3$		O	1
422	Me	H	$-C(=NH)CH_3$		O	2
423	Me	H	$-C(=NH)CH_3$		O	2
424	Me	H	H		O	1
425	Me	H	H		O	1
426	Me	H	H		O	1
427	Me	H	H		O	1
428	Me	H	H		O	1
429	Me	H	H		O	1
430	Me	H	H		O	1
431	Me	H	H		O	1
432	Me	H	H		O	1
433	Me	H	H		O	1
434	Me	H	H		O	2
435	Me	H	H		O	2
436	Me	H	H		O	2
437	Me	H	H		O	2
438	Me	H	H		O	2

No	R_1	R_2	R_3	R_4	X	m
439	Me	H	H		O	2
440	Me	H	H		O	2
441	Me	H	H		O	2
442	Me	H	H		O	2
443	Me	H	H		O	2
444	Me	H	H		O	1
445	Me	H	H		O	1
446	Me	H	H		O	1
447	Me	H	H		O	1
448	Me	H	H		O	1
449	Me	H	H		O	1
450	Me	H	H		O	1
451	Me	H	H		O	1
452	Me	H	H		O	2
453	Me	H	H		O	2
454	Me	H	H		O	2
455	Me	H	H		O	2
456	Me	H	H		O	2
457	Me	H	H		O	2

No	R_1	R_2	R_3	R_4	X	m
458	Me	H	H		O	2
459	Me	H			O	1
460	Me	H			O	1
461	Me	H			O	1
462	Me	H			O	1
463	Me	H			O	1
464	Me	H			O	1
465	Me	H			O	1
466	Me	H			O	1
467	Me	H			O	1
468	Me	H			O	1
469	Me	H			O	2
470	Me	H			O	2
471	Me	H			O	2
472	Me	H			O	2
473	Me	H			O	2
474	Me	H			O	2
475	Me	H			O	2
476	Me	H			O	2

No	R_1	R_2	R_3	R_4	X	m
	Me	H	CH_3		O	2
	Me	H	$C(=NH)CH_3$		O	2
479	Me	H	H	NH_2	NH	1
480	Me	H	H	$NHCH_3$	NH	1
481	Me	H	H	$N(CH_3)_2$	NH	1
482	Me	H	H	MeNEt	NH	1
483	Me	H	H	$N(Et)_2$	NH	1
484	Me	H	H	NH_2		2
485	Me	H	H	$NHCH_3$	NH	2
486	Me	H	H	$N(CH_3)_2$	NH	2
487	Me	H	H	MeNEt	NH	2
488	Me	H	H	NEt_2	NH	2
489	Me	H	H			2
490	Me	H	H		NH	2
491	Me	H	H		NH	2
492	Me	H	H			2
493	Me	H	H		NH	2
494	Me	H	H		NH	2
495	Me	H	H		NH	2

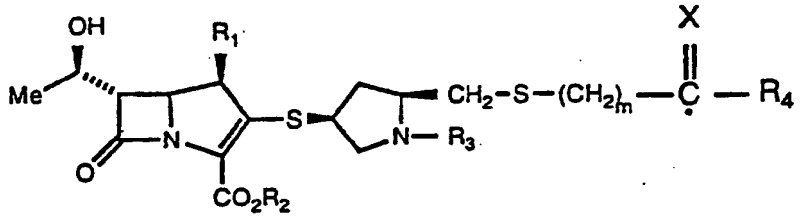
No	R_1	R_2	R_3	R_4	X	m
496	Me	H	H		NH	2
497	Me	H	H		NH	2
498	Me	H	H		NH	2
499	Me	H	H		NH	2
500	Me	H	H		NH	2
501	Me	H	H		NH	2
502	Me	H	H		NH	2
503	Me	H	H		NH	2
504	Me	H	H		NH	2



No	R_1	R_2	R_3	R_9	m
505	Me	H	H	OH	1
506	Me	H	H	OH	2
507	Me	H	H	OH	3
508	Me	H	H	OH	4
509	Me	H	H	OH	5
510	Me	H	H	OH	6
511	Me	H	H	$CH(OH)CH_3$	1
512	Me	H	H	$CH(OH)_2$	1
513	Me	H	H	$CH(OH)CH_3$	2
514	Me	H	H	$CH(OH)_2$	2
515	Me	H	H	$CH(OH)CH_3$	3
516	Me	H	H	$CH(OH)_2CH_3$	3
517	Me	H	H	$CH(OH)CH_3$	4
518	Me	H	H	$CH(OH)_2$	4
519	Me	H	$-C(=NH)H$	OH	1

No	R_1	R_2	R_3	R_9	m
520	Me	H	$-\underset{H}{C}=NH$	OH	2
521	Me	H	$-\underset{H}{C}=NH$	OH	3
522	Me	H	$-\underset{H}{C}=NH$	OH	4
523	Me	H	$-\underset{H}{C}=NH$	OH	5
524	Me	H	$-\underset{CH_3}{C}=NH$	OH	1
525	Me	H	$-\underset{CH_3}{C}=NH$	OH	2
526	Me	H	$-\underset{CH_3}{C}=NH$	OH	3
527	Me	H	$-\underset{CH_3}{C}=NH$	OH	4
528	Me	H	H	$OCONH_2$	1
529	Me	H	H	$OCONH_2$	2
530	Me	H	H	$OCONH_2$	3
531	Me	H	H	$OCONH_2$	4
532	Me	H	H	$OCONH_2$	5
533	Me	H	H	$OCONH_2$	6
534	Me	H	$-\underset{H}{C}=NH$	$OCONH_2$	1
535	Me	H	$-\underset{H}{C}=NH$	$OCONH_2$	2
536	Me	H	$-\underset{H}{C}=NH$	$OCONH_2$	3
537	Me	H	$-\underset{H}{C}=NH$	$OCONH_2$	4
538	Me	H	$-\underset{CH_3}{C}=NH$	$OCONH_2$	1
539	Me	H	$-\underset{CH_3}{C}=NH$	$OCONH_2$	2

No	R_1	R_2	R_3	R_9	m
540	Me	H	$-C(=NH)CH_3$	$OCONH_2$	3
541	Me	H	$-C(=NH)CH_3$	$OCONH_2$	4



No	R_1	R_2	R_3	R_4	X	m
542	Me	H	H	CH_2OH	O	1
543	Me	H	H	$(CH_2)_2OH$	O	1
544	Me	H	H	$(CH_2)_3OH$	O	1
545	Me	H	H	$(CH_2)_4OH$	O	1
546	Me	H	H	CH_2OH	O	2
547	Me	H	H	$(CH_2)_2OH$	O	2
548	Me	H	H	$(CH_2)_3OH$	O	2
549	Me	H	H	$(CH_2)_4OH$	O	2
550	Me	H	$-C(=NH)H$	$(CH_2)_2OH$	O	1
551	Me	H	$-C(=NH)CH_3$	$(CH_2)_2OH$	O	1
552	Me	H	$-C(=NH)H$	$(CH_2)_4OH$	O	2

No	R_1	R_2	R_3	R_4	X	m
553	Me	H	$-C(=NH)CH_3$	$(CH_2)_4OH$	O	2
554	Me	H	H	$(CH_2)_4OCH_3$	O	1
555	Me	H	H	$(CH_2)_2OCONH_2$	O	1
556	Me	H	H	$(CH_2)_3OCONH_2$	O	1
557	Me	H	H	$(CH_2)_4OCONH_2$	O	1
558	Me	H	H	CH_2OCONH_2	O	2
559	Me	H	H	$(CH_2)_2OCONH_2$	O	2
560	Me	H	H	$(CH_2)_3OCONH_2$	O	2
561	Me	H	H	$(CH_2)_4OCONH_2$	O	2
562	Me	H	$-C(=NH)H$	$(CH_2)_2OCONH_2$	O	2
563	Me	H	$-C(=NH)H$	$(CH_2)_3OCONH_2$	O	2
564	Me	H	$-C(=NH)H$	$(CH_2)_4OCONH_2$	O	2
565	Me	H	$-C(=NH)CH_3$	$(CH_2)_2OCONH_2$	O	2
566	Me	H	$-C(=NH)CH_3$	$(CH_2)_3OCONH_2$	O	2
567	Me	H	$-C(=NH)CH_3$	$(CH_2)_4OCONH_2$	O	2
568	H	H	H	CH_2OH	O	1
569	H	H	H	$(CH_2)_2OH$	O	1
570	H	H	H	$(CH_2)_3OH$	O	1
571	H	H	H	$(CH_2)_4OH$	O	1
572	H	H	H	$(CH_2)_2OH$	O	2

No	R_1	R_2	R_3	R_4	X	m
573	H	H	H	$(CH_2)_2OH$	O	2
574	H	H	H	$(CH_2)_3OH$	O	2
575	H	H	H	$(CH_2)_4OH$	O	2
576	H	H	H	$(CH_2)_2OCONH_2$	O	1
577	H	H	H	$(CH_2)_3OCONH_2$	O	1
578	H	H	H	$(CH_2)_4OCONH_2$	O	1
579	H	H	H	$(CH_2)_2OCONH_2$	O	2
580	H	H	H	$(CH_2)_3OCONH_2$	O	2
581	H	H	H	$(CH_2)_4OCONH_2$	O	2
582	H	H	H	NH_2	O	2

Reference Example 1

44.6g of 2-amino-2-methyl-1-propanol, 65g of diethyl-carbonate and 7g of potassium carbonate were mixed and stirred while heating at 120°C to 140°C, and then methanol produced during the reaction was removed with a water-trapping apparatus. The reaction solution was concentrated and then allowed to stand in a refrigerator to obtain a white precipitate. The resulting product was dissolved in ethyl ether and filtered to remove the insoluble materials. The filtrate was concentrated and then allowed to stand under ice-cooling to obtain a white solid which is then filtered and dried to obtain 25.7g of the desired product 4,4-dimethyl-oxazolidin-2-one.

Melting Point : 52-53°C

^{1}H NMR($DCCl_3$) δ : 1.35(s,6H,$2CH_3$), 4.00(s,2H,CH_2), 6.70(bs,1H,NH_1)

Reference Example 2

11.5g of the compound prepared in Reference Example 1 was dissolved in 200ml of anhydrous tetrahydrofuran and the resulting solution was cooled to -50°C to -60°C and 70ml of n-butyl lithium was slowly added thereto under nitrogen atmosphere. At the same temperature 22g of 2-bromopropionyl bromide was added dropwise thereto under stirring. After stirring for one hour at the same temperature, the reaction mixture was slowly warmed to 0°C and then stirred for one hour. The reaction mixture was diluted with water and then extracted with ethyl ether. The organic layer was combined, dried and concentrated under reduced pressure to obtain 18g of the desired product 3-(2-bromopropionyl)-4,4-dimethyl-oxazolidin-2-one.

^{1}H NMR($DCCl_3$) δ : 1.60(s,6H,$2CH_3$), 1.82(d,3H,CH_3),

4.05(s,2H,CH_2), 5.80(q,1H,CH,CH_3)

Reference Example 3

0.59g of azetinone and 0.5g of activated zinc were added to 40ml of anhydrous tetrahydrofuran. 1.06g of the compound prepared in Reference Example 2 was added dropwise thereto while heating under reflux and then the reaction mixture was heated for further 30 minutes under reflux. Saturated ammonium chloride solution was added to the mixture to complete the reaction. Ethyl acetate was added to the mixture to extract the reaction product and the extracted organic layers were combined, washed with distilled water, dried and concentrated under reduced pressure to obtain 470mg of the desired product (3S,4S)-3-(1R-t-butyldimethylsilyloxyethyl)-4-[(1R"-1-carboxyethyl)-2-(4",4"-dimethyl-2"-oxazolidinoyl)]azetidin-2-one.

Melting Point : 171-172°C

^{1}H NMR($DCCl_3$) δ : 0.07(s, 3H), 0.08(s,3H), 0.87(s,9H), 1.19(d,3H,J=6Hz), 1.21(d,3H,J=6Hz), 1.58(s,6H), 3.01-3.04(s,1H), 3.90-3.95 (m,1H), 4.14-4.23(m,2H), 6.00(s,1H,NH)

Reference Example 4

5.1g of the compound prepared in Reference Example 3 was dissolved in 200ml of tetrahydrofuran and then 3.5ml of 30% hydrogen peroxide was added thereto. Then, 1N-sodium hydroxide solution was slowly added dropwise to the reaction mixture with stirring at 5 to 10°C. The whole reaction mixture was stirred for 30 minutes at the same temperature, evaporated under reduced pressure to remove tetrahydrofuran solvent and extracted with ethyl acetate. The extract was adjusted to pH 3 to 4 by adding 10% hydrochloric acid solu-

tion and evaporated under reduced pressure to remove the solvent to obtain 2.6g of the white desired product (3S,4S)-3-[(1R-t-butyldimethylsilyloxyethyl)-4-(1R-1-carboxyethyl)]-azetidin-2-one.

Melting Point : 148.5-151.5°C

^{1}H NMR($CDCl_3$) δ : 0.07-0.08(s,6H), 0.89(s,9H), 1.19 (d,3H,J=6Hz), 1.27(d,3H,J=7Hz), 2.78-2.74(m,1H), 3.05(d,1H,J=4.4Hz,2H), 3.98(d,1H,J=4.82Hz), 4.25-4.17(m,2H), 6.50(s,1H,NH)

Reference Example 5

0.6g of the compound prepared in Reference Example 4 was dissolved in 5ml of anhydrous acetonitrile and the resulting solution was stirred for 30 minutes. Then 2.0g of magnesium p-nitrobenzylmalonate was added thereto and the mixture was stirred for 18 hours at 65°C. The reaction mixture was evaporated to remove the solvent and the residue was suspended in 50ml of ethyl acetate and then washed successively with 1N-hydrochloric acid solution, 10% potassium carbonate and saline. After removing the solvent, the residue was purified with column chromatography to obtain 70mg of the desired product (3S,4S)-3-[(R)-1-(t-butyldimethylsilyloxy)ethyl]-4-[(R)-1-(p-nitrobenzylacetoxy)carboxyethyl]azetidin-2-one.

^{1}H NMR($CDCl_3$) : 0.07(s,6H,CH3X2), 0.9(s,9H), 1.10(d,3H, CH_3), 1.23(d,3H,CHX3), 2.29(dd,1H), 2.92 (m,1H), 3.66(s,2H), 3.96(dd,1H), 4.20 (m,1H), 5.39(s,2H), 7.56 and 8.25(d, 2H,$\varnothing$).

Reference Example 6

2.87g of the compound prepared in Reference Example 5 was dissolved in 30ml of methanol and 3ml of 6N-hydrochloric acid solution was added thereto. The reaction mixture was stirred for 2 hours at room temperature and then adjusted to pH 7 to 8 with 0.1N-phosphate buffer and 10% potassium carbonate. After removing the solvent from the reaction mixture, the residue was extracted with ethyl acetate. The extract was washed with water and concentrated under reduced pressure. The residue was purified with column chromatography to obtain 1.7g of the desired product (3S,4S)-3-[(R)-1-(t-butyldimethylsilyloxy)ethyl]-4-[(R)-1-(p-nitrobenzylacetoxy)carboxyethyl]azetidin-2-one.

^{1}H NMR($CDCl_3$) δ : 1.30(d,6H), 2.90(dd,1H,CH), 2.94(q,1H, CH), 3.65-3.70(ABq,2H,CH_2), 3.84(dd,1H, CH), 4.15(m,1H,CH), 7.50 and 8.25(d, 2H,ϕ)

Reference Example 7

0.4g of the compound prepared in Reference Example 6 was dissolved in 5ml of anhydrous acetonitrile and to the resulting solution were added 7.4g of tosyl azide and 0.2g of triethylamine. The reaction solution was stirred for 2 hours at room temperature and then concentrated under reduced pressure. The residue was subjected to column chromatography to obtain 400mg of the desired product (3S,4S)-3-[(R)-1-hydroxyethyl]-4-[(R)-1-methyl-3-diazo-3-(p-nitrobenzyloxycarbonyl)-2-oxopropyl]azetidin-2-one.

^{1}H NMR($CDCl_3$) δ : 1.25(d,6H), 2.95(dd,1H), 3.77(q,1H, CH), 3.86(dd,1H,CH), 4.15(m,1H,CH), 5.38 (s,2H,CH_2), 7.55 and 8.30(d,2H,ϕ)

Reference Example 8

0.4g of the compound prepared in Reference Example 7 was added to 20ml of the mixed solvent of anhydrous ethyl acetate and anhydrous hexane and the resulting mixture was heated for one hour under reflux. A catalytic amount of rhodium acetate was added thereto under warming. The reaction mixture was stirred under reflux for one hour and then filtered with diatomaceous earth to remove the solvent to obtain 380mg of the desired product p-nitrobenzyl-(1R,5S,6S)-2-keto-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate.

^{1}H NMR($CDCl_3$) δ : 1.23(d,3H, β-methyl), 1.40(d,3H, CH_3CHOH), 2.86(q,1H,CH), 3.30(dd,1H,CH), 4.30(dd,1H,CH), 4.36(q,1H,CH), 4.78(s, 1H,CH), 5.28 and 5.42(ABq,2H,CH_2), 7.58 and 8.30(d,2H, ϕ)

Reference Example 9

13.2g of trans-4-hydroxy-L-proline was dissolved in 111ml of 2N-sodium hydroxide solution, and 23.76g of p-nitrobenzyloxycarbonylchloroformate dissolved in 20ml of methylene chloride was added thereto while stirring under ice-cooling and the mixture was stirred for 2 hours at the same temperature. Then 50ml of 2N-sodium hydroxide was added to the mixture to separate the layers. The organic layer was removed, and 18.5g of concentrated sulfuric acid was added to the aqueous layer to precipitate the product. The resulting product was filtered, washed with distilled water and dried to obtain the desired product trans-1-(p-nitrobenzyloxycarbonyl)-4-hydroxy-L-proline in the yield of 83%.

Melting Point : 132-135°C

IR(Nujol)cm^{-1} : 3300, 1738, 1660, 1665, 1520

Reference Example 10

120g of the compound prepared in Reference Example 9 was dissolved in 50ml of methanol and the resulting solution was added dropwise to 50ml of tetrahydrofuran. To this mixture was added dropwise 60ml of ethyl ether solution of diazomethane under nitrogen atmosphere while stirring with ice-cooling and the whole mixture was stirred for 20 hours. The reaction solution was concentrated under reduced pressure to obtain the desired product trans-1-(p-nitrobenzyloxycarbonyl)-4-hydroxy-L-proline methyl ester in the yield of 70%.

IR(Neat)cm^{-1} : 1748, 1695, 1518, 1438, 1360, 1250, 1175

Reference Example 11

5.18g of the compound prepared in Reference Example 10, 3.79g of trimethylamine and 3.77g of t-butyldimethylsilyl chloride were dissolved in 50ml of anhydrous dimethylformamide and the resulting solution was stirred for 3 hours at room temperature, diluted with distilled water and then extracted with ethyl acetate. The organic layer was separated and washed successively with distilled water, 1.0N-hydrochloric acid solution and saline, dried and concentrated under reduced pressure to obtain the desired product trans-1-[(p-nitrobenzyloxycarbonyl)-4-(4-(t-butyldi- methylsilyloxy)]-L-proline methyl ester in the yield of 68%.

$[\alpha]_D^{19}$ = -36.2° (C=1.00 $CHCl_3$)
IR(Neat)cm^{-1} : 1750, 1710, 1517, 1415, 1355, 1250, 1115
NMR($CDCl_3$) δ : 0.08(9H,s), 1.8-2.4(2H,m), 3.3-3.8(2H,m), 3.63(3H,s), 3.72(3H,s), 5.20(1H,J=14Hz), 5.23(1H,s), 7.42(2H,d,J=9Hz), 8.15(2H,d,J=9Hz)

Reference Example 12

5.64g of the compound prepared in Reference Example 11 was dissolved in 60ml of anhydrous tetrahydrofuran and 1.01g of sodium borohydride and 3.52g of calcium chloride were added to the resulting solution. The reaction solution was refluxed under heating for one hour and diluted with distilled water and then extracted with ethyl acetate. The organic layer was separated, washed with distilled water and saline, dried and concentrated under reduced pressure to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-(hydroxymethyl)-4-(t-butyldimethylsilyloxy)]pyrrolidine in the yield of 75%.

$[\alpha]_D^{19}$ = -40.1° (C=1.00 $CHCl_3$)

IR(Neat)cm^{-1} : 1670, 1504, 1420, 1405, 1240, 1100

NMR($CDCl_3$) δ : 0.07(6H,s), 0.87(9H,s), 1.4-2.1(2H,m), 3.38-3.84(4H,m), 3.9-4.5(2H,m), 5.22(2H,s), 7.47(2H,d,J=9Hz), 8.17(2H,d,J=9Hz)

Reference Example 13

32.6g of the compound prepared in Reference Example 12 was dissolved in 64ml of anhydrous pyridine and 28g of p-toluenesulfonyl chloride was added to the resulting solution and then the mixture was stirred for 12 hours at room temperature. The reaction solution was diluted with distilled water and then extracted with ethyl acetate. The organic layer was separated, washed with saline, 1.0N hydrochloric acid solution and distilled water, dried and concentrated under reduced pressure to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-(p-toluenesulfonyloxymethyl)-4-(t-butyldimethylsilyloxy)]pyrrolidine in the yield of 75%.

IR(Neat)cm^{-1} : 1700, 1518, 1342, 1265, 1172, 1090

Reference Example 14

35.8g of the compound prepared in Reference Example 13 and 19g of sodium iodide were added to 90ml of methylethylketone and the mixture was refluxed under heating. The reaction solution was cooled to room temperature and then filtered. The filtrate was concentrated under reduced pressure and the residue was dissolved in ethyl acetate, washed with each of distilled water and saline, dried and concentrated under reduced pressure to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-(iodomethyl)-4-(t-butyldimethylsilyloxy)]-pyrrolidine in the yield of 70%.

Melting Point : 88-92°C
IR(Neat)cm^{-1} : 1700, 1512, 1405, 1353, 1248
NMR($CDCl_3$) δ : 0.07(6H,s), 0.87(9H,s), 1.4-2.5(2H,m), 3.1-3.8(4H,m), 3.95-4.38(2H,m), 5.22(2H,s), 7.5-8.3(4H,d,J=9Hz)

Reference Example 15-A

5g of the compound prepared in Reference Example 14 was dissolved in 50ml of dimethylformamide, and then 2g of 3-mercaptopropionate ethyl ester, 1.7g of calcium iodide and 1.7g of triethylamine were added to the resulting solution while stirring. The reaction mexture was warmed to 60°C to 70°C and allowed to react for 4 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, washed several times with distilled water and then washed with 1N hydrochloric acid solution and saline, dried and concentrated under reduced pressure to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-(ethyloxycarbonylethylthiomethyl)-4-(t-butyldimethylsilyloxy)]pyrrol-

idine in the yield of 60%.

IR(Neat)cm^{-1} : 1745, 1705, 1695, 1510, 1405, 1342
NMR($CDCl_3$) δ : 0.07(6H,s), 0.9(9H,s), 1.55-2.5(4H,m), 3.0(3H,s), 3.15-3.8(4H,m), 3.95-4.25(4H,m), 5.22(2H,s), 7.25-8.35(9H,d,J=9Hz)

Reference Example 15-B

11g of the compound prepared in Reference Example 15-A was dissolved in 20ml of methanol, and 30ml of 2N-sodium hydroxide solution was added to the resulting solution while stirring under ice-cooling. The reaction mixture was stirred for 30 minutes, adjusted to neutral pH value by adding 1N-acetic acid and then evaporated under reduced pressure to remove the solvent. The residue was extracted with ethyl acetate. The extract was dried, concentrated under reduced pressure and then subjected to column chromatography to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-(hydroxycarbonylethylthiomethyl)-4-(t-butyldimethylsilyloxy)]pyrrolidine in the yield of 85%.

IR(Neat)cm^{-1} : 3500, 1725, 1690, 1425, 1350
NMR($CDCl_3$) δ : 0.08(6H,s), 0.87(9H,s), 1.45-2.20(4H,m), 3.10-3.50(4H,m), 5.22(2H,s), 7.25-8.5(4H,d,J=8Hz)

Reference Example 15-C

4g of the compound prepared in Reference Example 15-B was dissolved in 40ml of anhydrous acetonitrile and 1.56g of carbonyldiimidazole was added to the resulting solution under ice-cooling. The mixture was stirred for 30 minutes and 2.7g of triethylamine and 1.06g of glycinamide hydrochloride were added thereto. The whole mixture was stirred for 2 hours under ice-cooling and then for one hour at room

temperature. The reaction solution was diluted with ethyl acetate, washed successively with distilled water, 1N-hydrochloric acid solution, 5% sodium bicarbonate solution and saline, dried and then concentrated under reduced pressure. The residue was subjected to column chromatography eluting with ethyl acetate:n-hexane (1:1) to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-(carbamoylmethylcarbamoylethylthiomethyl)-4-(t-butyldimethylsilyloxy)]-pyrrolidine in the yield of 65%.

IR(Neat)cm^{-1} : 1725, 1710, 1695, 1515, 1420, 1325
NMR($CDCl_3$) δ : 0.07(6H,s), 0.8(9H,s), 1.25-1.45(2H,m), 2.25-2.50(4H,m), 3.95-4.25(2H,m), 5.25 (2H,s), 7.5-8.5(4H,d,J=8Hz)

Reference Example 15-D

2.93g of the compound prepared in Reference Example 15-C was dissolved in 15ml of methanol and 2ml of 6N-hydrochloric acid solution was added to the resulting solution while stirring under ice-cooling. The mixture was stirred for 2 hours at the same temperature. The reaction solution was concentrated under reduced pressure and the residue was extracted with ethyl acetate. The extract was dried and then concentrated under reduced pressure to remove the solvent. The residue was subjected to column chromatography eluting with ethyl acetate:n-hexane (3:1) to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-(carbamoylmethylcarbamoylethylthiomethyl)-4-(hydroxy)]pyrrolidine in the yield of 93.3%.

IR(Neat)cm^{-1} : 3600, 1720, 1700, 1690, 1510, 1420
NMR($CDCl_3$) δ : 1.80-2.18(2H,m), 2.65-3.05(2H,m), 3.09(2H, s), 3.30-3.35(2H,m), 3.85-4.50(2H,m), 4.96-5.24(2H,d,J=8Hz), 7.66-8,26(4H,d,J=8Hz)

Reference Example 15-E

2.17g of the compound prepared in Reference Example 15-D was dissolved in 30ml of anhydrous dichloromethane and 0.59 of methanesulfonyl chloride and 0.71g of triethylamine were added to the resulting solution while stirring under ice-cooling. Then, the mixture was stirred for 2 hours at the same temperature. The reaction solution was then washed with distilled water, 1N hydrochloric acid solution and saline, dried and concentrated under reduced pressure to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-(carbamoylmethylcarbamoylethylthiomethyl)-4-(mesyloxy)]pyrrolidine in the yield of 66.1%.

IR(Neat)cm^{-1} : 1710, 1700, 1690, 1510, 1435, 1350, 1050
NMR($CDCl_3$) δ : 2.05-2.60(3H,m), 3.03(3H,s), 5.25(2H,s), 7.53(2H,d,J=8Hz), 8.25(2H,d,J=8Hz)

Reference Example 15-F

To 20ml of dimethylformamide were added 2g of the compound prepared in Reference Example 15-E and 0.57g of potassium thioacetate and then the reaction mixture was stirred for 4 hours at 70 to 80°C. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and then washed several times with distilled water, dried and concentrated under reduced pressure. The residue was subjected to column chromatography eluting with ethyl acetate to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-(carbamoylmethylcarbamoylethylthiomethyl)-4-(acetylthio)]pyrrolidine in the yield of 65.2%.

IR(Neat)cm^{-1} : 1725, 1710, 1690, 1510, 1420, 1350
NMR($CDCl_3$) δ : 2.40-3.15(4H,m), 3.25(3H,s), 3.75-4.50 (4H,m), 5.23(2H,s), 7.25-8.23(4H,d,J=8Hz)

Reference Example 15-G

1.5g of the compound prepared in Reference Example 15-F was dissolved in 15ml of methanol and 0.2g of sodium methoxide was added to the resulting solution while stirring under ice-cooling. The mixture was stirred for 15 minutes at the same temperature. The reaction mixture was added to acetic acid to neutralize and then concentrated under reduced pressure. The residue was extracted with ethyl acetate. The extract was dried and then concentrated under reduced pressure to obtain the desired product (2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-(carbamoylmethylcarbamoylethylthiomethyl)-4-mercaptopyrrolidine in the yield of 85.2%.

IR(Neat)cm^{-1} : 1710, 1690, 1510, 1425
NMR($CDCl_3$) δ : 1.75-1.95(3H,m), 2.45-2.85(2H,m), 2.90-3.15(2H,m), 3.21(2H,s), 3.25-4.30(4H,m), 5.24(2H,s), 7.55-8.27(4H,d,J=8Hz)

Reference Example 16-A

The reaction was carried out in the same manner as that of Reference Example 15-A, using 7g of the compound prepared in Reference Example 14, 1.8ml of ethylthioglyconate, 2.7g of calcium iodide and 2.1ml of triethylamine to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-(ethyloxycarbonylmethylthiomethyl)-4-(t-butyldimethylsilyloxy)]-pyrrolidine in the yield of 75%.

IR(Neat)cm^{-1} : 1745, 1700, 1690, 1515, 1410
NMR($CDCl_3$) δ : 0.07(6H,s), 0.9(9H,s), 1.50-1.98(2H,m), 2.02-2.25(2H,m), 3.0(3H,s), 3.15-3.8(2H,m), 3.95-4.25(4H,m), 5.22(2H,s), 7.25-8.35(4H,d,J=8Hz)

Reference Example 16-B

3g of the compound prepared in Reference Example 16-A was treated in the same manner as that of Reference Example 15-B to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-(hydroxycarbonylmethylthiomethyl)-4-(t-butyldimethylsilyloxy)]pyrrolidine in the yield of 60%.

IR(Neat)cm^{-1} : 3600, 1720, 1695, 1520, 1420

NMR($CDCl_3$) δ : 0.08(6H,m), 0.85(9H,s), 1.45-2.20(2H,m), 3.10-3.45(4H,m), 5.22(2H,s), 7.25-8.5 (4H,d,J=8Hz)

Reference Example 16-C

5g of the compound prepared in Reference Example 16-B was dissolved in 30ml of anhydrous acetonitrile solution and 2g of carbonyldiimidazole was added to the resulting solution while stirring under ice-cooling. After stirring the mixture, 3.0g of triethylamine and 1.5g of glycinamide hydrochloride were successively added thereto and the reaction mixture was then treated in the same manner as that of Reference Example 15-C to obtain the desired product (2S, 4S)-[1-(p-nitrobenzyloxycarbonyl)-2-(carbamoylmethylcarbamoylmethylthiomethyl)-4-(t-butyldimethylsilyloxy)]pyrrolidine in the yield of 80%.

IR(Neat)cm^{-1} : 1720, 1705, 1695, 1570

NMR($CDCl_3$) δ : 0.06(6H,s), 0.86(9H,s), 1.88-2.22(2H,m), 3.22(2H,s), 5.25(2H,s), 7.53(2H,d,J=8Hz), 8.25(2H,d,J=8Hz)

Reference Example 16-D

3.2g of the compound prepared in Reference Example 16-B was treated in the same manner as that of Reference Example 15-C to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-(carbamoylmethylcarbamoylmethylthiomethyl)-4-(hydroxy)]pyrrolidine in the yield of 85.2%.

IR(Neat)cm^{-1} : 3600, 1715, 1700, 1510, 1400
NMR($CDCl_3$) δ : 1.80-2.10(2H,m), 2.65-3.05(2H,m), 3.09(2H, s), 3.30-3.55(2H,m), 3.85-4.50(2H,m), 4.95-5.24(2H,s), 7.66-8.26(4H,d,J=8Hz)

Reference Example 16-E

2g of the compound prepared in Reference Example 16-D was dissolved in 30ml of anhydrous dichloromethane, and 0.75g of triethylamine and 0.6g of methanesulfonyl chloride were added to the resulting solution. Then, the reaction mixture was treated in the same manner as that of Reference Example 15-E to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-(carbamoylmethylcarbamoylmethylthiomethyl)-4-(mesyloxy)]pyrrolidine in the yield of 72%.

IR(Neat)cm^{-1} : 1715, 1700, 1695, 1500, 1410, 1355
NMR($CDCl_3$) δ : 2.05-2.60(3H,m), 3.03(3H,s), 5.25(2H,s), 7.53-8.25(4H,d,J=8Hz)

Reference Example 16-F

1.9g of the compound prepared in Reference Example 16-E was added to 15ml of dimethylformamide and 0.5g of potassium thioacetate and the resulting mixture was treated in the same manner as that of Reference Example 15-E to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-(carbamoylmethylcarbamoylmethylthiomethyl)-4-(acetylthio)]pyrrolidine in the yield of 57%.

IR(Neat)cm^{-1} : 1725, 1750, 1695, 1500
NMR($CDCl_3$) δ : 2.40-3.15(4H,m), 3.21(3H,s), 3.75-4.50(5H, m), 5.23(2H,s), 7.59-8.23(4H,d,J=8Hz)

Reference Example 16-G

2.0g of the compound prepared in Reference Example 16-F was dissolved in 18ml of methanol and 0.25g of sodium methoxide was added to the resulting solution while stirring under ice-cooling. The reaction mixture was then treated in the same manner as that of Reference Example 15-G to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-(carbamoylmethylcarbamoylmethylthiomethyl)-4-(mercapto)]pyrrolidine in the yield of 78%.

IR(Neat)cm^{-1} : 1710, 1695, 1520, 1425, 1350
NMR($CDCl_3$) δ : 1.75-1.95(3H,m), 2.45-2.85(2H,m), 2.90-3.15 (2H,m), 3.21(2H,s), 3.25-3.50(2H,m), 3.85-4.30(2H,m), 5.24(2H,s), 7.55-8.27(4H,d, J=8Hz)

Reference Example 17-A

4g of the compound prepared in Reference Example 14 was dissolved in 40ml of anhydrous acetonitrile and 1.56g of carbonyldiimidazole was added to the resulting solution. After stirring the mixture for 30 minutes, 2.7g of triethylamine and 2.3g of aminoacetonitrile hydrochloride were added thereto and the whole mixture was stirred for 2 hours under ice-cooling and then one hour at room temperature. The reaction solution was diluted with ethyl acetate, washed successively with distilled water, 1N-hydrochloric acid solution, 5% sodium bicarbonate solution and saline, dried and then concentrated under reduced pressure. The residue was subjected to column chromatography eluting with ethyl acetate:n-hexane (2:1) to obtain the desired product

(2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-(cyanomethylcarbamoylethylthiomethyl)-4-(t-butyldimethylsilyloxy)]pyrrolidine in the yield of 65%.

IR(Neat)cm^{-1} : 2250, 1725-1710, 1690-1665
NMR($CDCl_3$) δ : 0.05(6H,s), 0.86(9H,s), 1.80-2.15(4H,m), 5.25(2H,s), 7.25-8.21(4H,d,J=8Hz)

Reference Example 17-B

3.5g of the compound prepared in Reference Example 17-A was dissolved in 15ml of methanol and 2ml of 6N-hydrochloric acid solution was added to the resulting solution while stirring under ice-cooling. The reaction solution was stirred for 2 hours at the same temperature and concentrated under reduced pressure. The residue was extracted with ethyl acetate and the extract was dried and then concentrated under reduced pressure to remove the solvent. The residue was subjected to column chromatography eluting with ethyl acetate:n-hexane (3:1) to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-(cyanomethylcarbamoylethylthiomethyl)-4-(hydroxy)]pyrrolidine in the yield of 87.5%.

IR(Neat)cm^{-1} : 2250, 1710, 1695-1675, 1610, 1525
NMR($CDCl_3$) δ : 1.52-1.95(2H,m), 2.75-3.50(2H,m), 4.05-4.75(4H,m), 5.23(2H,s), 7.53-8.22(4H,d, J=8Hz)

Reference Example 17-C

2.78g of the compound prepared in Reference Example 17-B was dissolved in 30ml of anhydrous dichloromethane and 0.62g of methanesulfonyl chloride and 1.4g of triethylamine were added to the resulting solution while stirring under ice-cooling. The mixture was stirred for 2 hours at the

same temperature. The reaction solution was washed with distilled water, 1N-hydrochloric acid solution and saline, dried and then concentrated under reduced pressure to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-(cyanomethylcarbamoylethylthiomethyl)-4-(mesyloxy)]pyrrolidine in the yield of 72.5%.

IR(Neat)cm^{-1} : 2250, 1710, 1700, 1690, 1510, 1435, 1350, 1050

NMR($CDCl_3$) δ : 2.05-2.80(4H,m), 3.03(3H,m), 7.53-8.25 (4H,d,J=8Hz)

Reference Example 17-D

2.8g of the compound prepared in Reference Example 17-C was added to 20ml of dimethylformamide and then 0.65g of potassium thioacetate was added thereto. The reaction mixture was stirred for 4 hours at 70 to 80°C and then cooled to room temperature, diluted with ethyl acetate, washed several times with distilled water, dried and concentrated under reduced pressure. The residue was subjected to column chromatography eluting with ethyl acetate to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-(cyanomethylcarbamoylethylthiomethyl)-4-(acetylthio)]pyrrolidine in the yield of 73.5%.

NMR($CDCl_3$) δ : 1.75-2.40(4H,m), 3.25-4.55(6H,m), 7.85-8.10 (4H,d,J=8Hz)

Reference Example 17-E

0.9g of the compound prepared in Reference Example 17-D was dissolved in 15ml of methanol, and 0.1g of sodium methoxide was added to the resulting solution while stirring under ice-cooling. The reaction solution was stirred for 15 minutes at the same temperature, neutralized with acetic

acid and then concentrated under reduced pressure. The residue was extracted with ethyl acetate and the extract was dried and concentrated under reduced pressure to obtain the desired product (2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-(cyanomethylcarbamoylethylthiomethyl)-4-mercaptopyrrolidine in the yield of 63.8%.

IR(Neat)cm^{-1} : 1720-1690, 1605, 1530-1515
NMR($CDCl_3$) δ : 1.65-1.94(3H,m), 2.45-2.85(2H,m), 2.90-3.30 (4H,m), 3.25-3.50(2H,m), 5.24(2H,s), 7.55-8.24(4H,d,J=8Hz)

Reference Example 18-A

6g of the compound prepared in Reference Example 14 was dissolved in 40ml of anhydrous acetonitrile and 2.5g of carbonyldiimidazole was added to the resulting solution while stirring under ice-cooling. After stirring the mixture, 3.5g of triethylamine and 2.1g of aminoacetonitrile hydrochloride were successively added thereto. Then, the subsequent reaction was carried out in the same manner as that of Reference Example 15-C to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-(cyanomethylcarbamoylmethylthiomethyl)-4-(t-butyldimethylsilyloxy)]pyrrolidine in the yield of 88.5%.

IR(Neat)cm^{-1} : 2250, 1735-1710, 1695-1665, 1610
NMR($CDCl_3$) δ : 0.06(6H,s), 0.85(9H,s), 1.75-2.10(4H,m), 5.25(2H,s), 7.30-8.56(4H,d,J=8Hz)

Reference Example 18-B

2.5g of the compound prepared in Reference Example 18-A was treated in the same manner as that of Reference Example 15-D to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-(cyanomethylcarbamoylmethylthiomethyl)-4-

(hydroxy)]pyrrolidine in the yield of 90.8%.

IR(Neat)cm^{-1} : 2250, 1745-1710, 1690-1675
NMR($CDCl_3$) δ : 1.75-2.25(2H,m), 2.55-3.10(2H,m), 3.90(2H,s), 3.30-3.45(3H,m), 4.95-5.24(2H,s), 7.66-8.25(4H,d,J=8Hz)

Reference Example 18-C

2.5g of the compound prepared in Reference Example 18-B was dissolved in 30ml of anhydrous dichloromethane and 0.8g of methanesulfonyl chloride and 1.0g of triethylamine were added to the resulting solution while stirring under ice-cooling. The resulting reaction mixture was treated in the same manner as that of Reference Example 15-E to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-(cyanomethylcarbamoylmethylthiomethyl)-4-(mesyloxy)]pyrrolidine in the yield of 72%.

IR(Neat)cm^{-1} : 2250, 1725-1690, 1660, 1610
NMR($CDCl_3$) δ : 2.10-2.45(3H,m), 3.03(3H,s), 5.25(2H,s), 7.53-8.25(4H,d,J=8Hz)

Reference Example 18-D

2.5g of the compound prepared in Reference Example 18-C was added to 15ml of dimethylformamide and 0.8g of potassium thioacetate and then the reaction mixture was treated in the same manner as that of Reference Example 15-E to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-(cyanomethylcarbamoylmethylthiomethyl)-4-(acetylthio)]pyrrolidine in the yield of 63.5%.

IR(Neat)cm^{-1} : 2250, 1725, 1750, 1695, 1500
NMR($CDCl_3$) δ : 2.15-3.00(4H,m), 3.2(3H,s), 3.75-4.50 (5H,m), 5.23(2H,s), 7.59-8.23(4H,d,J=8Hz)

Reference Example 18-E

1.8g of the compound prepared in Reference Example 18-D was dissolved in 18ml of methanol, and 0.25g of sodium methoxide was added to the resulting solution while stirring under ice-cooling. The reaction mixture was treated in the same manner as that of Reference Example 15-G to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-(cyanomethylcarbamoylmethylthiomethyl)-4-(mercapto)]pyrrolidine in the yield of 65.8%.

IR(Neat)cm^{-1} : 2250, 1735-1710, 1695-1675, 1610

NMR($CDCl_3$) δ : 1.65-1.75(3H,m), 2.45-2.85(2H,m), 2.90-3.30(5H,m), 3.50(2H,m), 5.24(2H,s), 7.55-8.27(4H,d,J=8Hz)

Reference Example 19-A

52g of the compound prepared in Reference Example 14 and 18.3g of potassium thioacetate were added to 50ml of dimethylformamide and the mixture was warmed to 60 to 75°C and stirred for 2 hours. The reaction solution was cooled to room temperature, diluted with distilled water and extracted with ethyl acetate. The organic layer was washed with distilled water, saline and 5% sodium bicarbonate solution, dried and concentrated under reduced pressure to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-(acetylthiomethyl)-4-(t-butyldimethylsilyloxy)]pyrrolidine in the yield of 55%.

IR(Neat)cm^{-1} : 1710-1700, 1610, 1530

NMR($CDCl_3$) δ : 0.06(6H,s), 1.84(9H,s), 2.35(3H,s), 5.26(2H,s), 7.54-8.22(4H,d,J=8Hz)

Reference Example 19-B

5g of the compound prepared in Reference Example 19-A was dissolved in 10ml of methanol and 2ml of 28% sodium methoxide was added to the resulting solution while stirring under ice-cooling. The mixture was stirred for 15 minutes under nitrogen atmosphere and then 1g of 2-iodoethanol dissolved in 10ml of methanol was added dropwise thereto at the same temperature. The reaction mixture was stirred for 4 hours at the same temperature and concentrated under reduced pressure to remove the solvent. The residue was dissolved in ethyl acetate, washed with distilled water, dried and then concentrated under reduced pressure to remove the solvent to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-(hydroxyethylthiomethyl)-4-(t-butyldimethylsilyloxy)]pyrrolidine in the yield of 50%.

IR(Neat)cm^{-1} : 1710, 1690-1675, 1610, 1525

NMR($CDCl_3$) δ : 0.06(6H,s), 0.86(9H,s), 1.88-2.22(2H,m), 3.22(2H,s), 5.25(2H,s), 7.53-8.29 (4H,d,J=8Hz)

Reference Example 19-C

850mg of the compound prepared in Reference Example 19-B and 1ml of 6N-hydrochloric acid solution were added to 8ml of methanol and the mixture was stirred for one hour, diluted with ethyl acetate, washed with distilled water, dried and then concentrated under reduced pressure. The residue was purified with column chromatography to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-(acetoxyethylthiomethyl)-4-(hydroxy)]pyrrolidine in the yield of 70%.

IR($CHCl_3$)cm^{-1} : 1710, 1610, 1525

NMR(DMSO-d_6) δ : 1.80-2.15(2H,m), 2.65-3.05(2H,m), 3.09 (2H,s), 3.30-3.55(2H,m), 5.24(2H,s), 7.66-8.26(2H,d,J=8Hz)

Reference Example 19-D

1.5g of the compound prepared in Reference Example 19-C, 2.2g of triphenylphosphine and 5g of diethylazodicarboxylate were respectively added to 20ml of anhydrous tetrahydrofuran solution, and the mixture was stirred for 2 hours under ice-cooling. 1.2g of thiolacetic acid was added to the reaction mixture at the same temperature and the mixture was stirred for 2 hours. The reaction solution was increased to room temperature and then stirred for 20 hours, evaporated under reduced pressure, diluted with ethyl acetate, washed with distilled water, dried and then concentrated under reduced pressure. The residue was purified with column chromatography to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-(acetoxyethylthiomethyl)-4-(acetylthio)]pyrrolidine in the yield of 70%.

IR(Neat)cm^{-1} : 1745, 1710, 1600, 1510, 1398, 1360, 1098
NMR($CDCl_3$) δ : 1.75-1.95(3H,m), 2.45-2.85(1H,m), 2.90-3.15(2H,m), 3.21(2H,s), 3.25-3.50(2H,m), 3.58-4.30(2H,m), 5.24(2H,s), 7.55-8.27 (4H,d,J=8Hz)

Reference Example 20-A

5g of the compound prepared in Reference Example 19-A was dissolved in 10ml of methanol, and 2ml of 28% sodium methoxide was added to the resulting solution under ice-cooling. The mixture was stirred for 15 minutes under nitrogen atmosphere. To this mixture was added 1g of 2-iodoethanol dissolved in 10ml of methanol at the same temperature. The reaction mixture was stirred for 4 hours at

the same temperature and concentrated under reduced pressure to remove the solvent. The residue was dissolved in ethyl acetate, washed with distilled water, dried and concentrated under reduced pressure to remove the solvent to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-(hydroxyethylthiomethyl)-4-(t-butyldimethylsilyloxy)]pyrrolidine in the yield of 50%.

IR(Neat)cm^{-1} : 3600, 1740, 1690, 1523, 1400, 1345
NMR($CDCl_3$) δ : 0.06(6H,s), 0.86(9H,s), 1.51-2.1(2H,m), 2.4-2.9(2H,m), 3.22(2H,s), 5.25(2H,s), 7.53-8.25(4H,d,J=8Hz)

Reference Example 20-B

1.5g of the compound prepared in Reference Example 20-A was dissolved in 15ml of anhydrous pyridine and 0.8ml of acetic anhydride and 0.3g of dimethylaminopyridine were added to the resulting solution. The mixture was stirred for one hour at room temperature, diluted with ethyl acetate, washed with distilled water and then concentrated under reduced pressure. The residue was purified with column chromatography to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-(acetoxyethylthiomethyl)-4-(t-butyldimethylsilyloxy)]pyrrolidine in the yield of 70%.

IR(Neat)cm^{-1} : 1740, 1725-1710, 1690, 1610
NMR($CDCl_3$) δ : 0.06(6H,s), 0.8(9H,s), 1.52-1.95(2H,m), 2.4-2.65(2H,m), 3.15-3.35(3H,s), 5.25 (2H,s), 7.53-8.25(4H,d,J=8Hz)

Reference Example 20-C

850mg of the compound prepared in Reference Example 20-B and 1ml of 6N-hydrochloric acid solution were added to 8ml of methanol. The reaction mixture was stirred for one hour

at room temperature, diluted with 20ml of ethyl acetate, washed with distilled water, dried and concentrated under reduced pressure. The residue was purified with column chromatography to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-(acetoxyethylthiomethyl)-4-(hydroxy)]pyrrolidine in the yield of 70%.

IR(Neat)cm^{-1} : 3600, 1720, 1680, 1510, 1410, 1342, 1225
NMR($CDCl_3$) δ : 1.52-1.95(2H,m), 2.75-2.95(2H,m), 3.35 (3H,s), 4.05-4.75(2H,m), 5.25(2H,s), 7.53-8.22(4H,d,J=8Hz)

Reference Example 20-D

1.5g of the compound prepared in Reference Example 20-C, 2.2g of triphenylphosphine and 5g of diethylazodicarboxylate were added to 20ml of anhydrous tetrahydrofuran solution. The mixture was stirred for 2 hours under ice-cooling, and 1.2g of thiolacetic acid was added thereto at the same temperature. The reaction mixture was increased to room temperature and then stirred for 20 hours, evaporated under reduced pressure, diluted with ethyl acetate, washed with distilled water and then concentrated under reduced pressure. The residue was purified with column chromatography to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-(acetoxyethylthiomethyl)-4-(acetylthio)]-pyrrolidine in the yield of 70%.

IR(Neat)cm^{-1} : 1745, 1710, 1600, 1510, 1398, 1360, 1098

Reference Example 20-E

300mg of the compound prepared in Reference Example 20-D was dissolved in 5ml of methanol and 2ml of 1N sodium hydroxide solution was added to the resulting solution. The mixture was stirred for 20 minutes in nitrogen atmosphere

under ice-cooling and then 2ml of 1N hydrochloric acid solution was added thereto. The reaction solution was concentrated under reduced pressure, and the residue was dissolved in ethyl acetate, washed with distilled water and saline, dried, and then concentrated under reduced pressure to obtain an oily residue. This oily residue was purified with column chromatography to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-(hydroxyethylthiomethyl)-4-(mercapto)]pyrrolidine in the yield of 46%.

IR(Neat)cm^{-1} : 3600, 1725, 1680, 1522, 1433, 1410, 1350
NMR($CDCl_3$) δ : 1.85-2.22(2H,m), 2.65-3.05(2H,m), 3.09(2H,m), 3.30-3.55(2H,m), 3.85-4.50 (2H,m), 5.24(2H,s), 7.66-8.26(4H,d,J=8Hz)

Reference Example 21-A

4g of the compound prepared in Reference Example 15-B was dissolved in 50ml of anhydrous acetonitrile and 1.56g of carbonyldiimidazole was added to the resulting solution under ice-cooling. The reaction mixture was stirred for 30 minutes and 2.5g of triethylamine and 2g of 4-aminoacetyloxyethylpiperazine were added thereto. The whole mixture was stirred for 2 hours under ice-cooling and then for 4 hours at room temperature to complete the reaction. The reaction solution was diluted with ethyl acetate, washed with distilled water, 1N-hydrochloric acid solution, 5% sodium bicarbonate solution and saline, dried and then concentrated under reduced pressure. The residue was subjected to column chromatography eluting with ethyl acetate:n-hexane (1:3) to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-{(acetyloxyethylpiperazinylcarbamoyl)ethylmercaptomethyl}-4-(t-butyldimethylsilyloxy)]pyrrolidine in the yield of 68%.

IR(Neat)cm^{-1} : 1740, 1710-1690, 1550
NMR($CDCl_3$) δ : 0.07(6H,s), 0.8(9H,s), 1.25-1.55(4H,m),

2.10-2.50(4H,m), 5.25(2H,s), 7.5-8.5 (4H,d,J=8Hz)

Reference Example 21-B

3.15g of the compound prepared in Reference Example 21-A was dissolved in 15ml of methanol, and 1.5ml of 6N-hydrochloric acid solution was added to the resulting solution while stirring under ice-cooling. The reaction solution was stirred for 2 hours at the same temperature and then concentrated under reduced pressure. The residue was extracted with ethyl acetate, dried and then concentrated under reduced pressure to remove the solvent. The residue was subjected to column chromatography eluting with ethyl acetate:n-hexan (3:1) to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-{(acetyloxyethylpiperazinyl)carbamoylethylthiomethyl}-4-(hydroxy)]pyrrolidine in the yield of 87.2%.

IR(Neat)cm^{-1} : 3600, 1720, 1690, 1420
NMR($CDCl_3$) δ : 1.80-2.10(2H,m), 2.65-3.05(4H,m), 3.90 (2H,s), 3.30-3.35(2H,m), 4.96-5.29 (2H,d,J=8Hz), 7.66-8.26(4H,d,J=8Hz)

Reference Example 21-C

1.85g of the compound prepared in Reference Example 21-B was dissolved in 30ml of anhydrous dichloromethane, and 0.45g of methanesulfonyl chloride and 0.62g of triethylamine were added to the resulting solution. The reaction solution was stirred for 2 hours at the same temperature, washed with distilled water, 1N-hydrochloric acid solution and saline, dried and then concentrated under reduced pressure to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-{(acetyloxypiperazinylcarbamoyl)ethylthiomethyl}-4-(mesyloxy)]pyrrolidine in the yield of 68.5%.

IR(Neat)cm^{-1} : 1745, 1710-1695, 1610, 1580
NMR($CDCl_3$) δ : 2.10-2.55(4H,m), 3.30-3.33(3H,m), 5.25 (2H,s), 7.58(2H,d,J=8Hz), 8.25(2H,d,J=8Hz)

Reference Example 21-D

2g of the compound prepared in Reference Example 21-C was added to 20ml of dimethylformamide, and 0.57g of potassium thioacetate was added thereto. The reaction mixture 4was stirred for 4 hours at 70 to 80°C and then cooled to room temperature. Then, the mixture was diluted with ethyl acetate, washed several times with distilled water, dried and then concentrated under reduced pressure. The residue was subjected to column chromatography eluting with ethyl acetate to obtain the desired product (2S,4S)-[1-(p-nitrobenzyl- oxycarbonyl)-2-{(acetyloxyethylpiperazinyl)carbamoylethylthiomethyl}-4-(acetylthio)]pyrrolidine in the yield of 65.2%.

IR(Neat)cm^{-1} : 1725, 1710, 1690, 1510, 1420, 1350
NMR($CDCl_3$) δ : 2.55-3.15(4H,m), 3.25-3.35(3H,m), 3.75-4.50(4H,m), 5.23(2H,s), 7.25-8.55 (4H,d,J=8Hz)

Reference Example 21-E

2.0g of the compound prepared in Reference Example 21-D wad dissolved in 15ml of methanol, and 0.21g of sodium methoxide was added to the resulting solution while stirring under ice-cooling. The mixture was stirred for 15 minutes at the same temperature and then neutralized with acetic acid. The reaction solution was concentrated under reduced pressure. The residue was extracted with ethyl acetate, dried and concentrated under reduced pressure to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-

[(hydroxyethylpiperazinylcarbamoyl)ethylthiomethyl]-4-mercatopyrrolidine in the yield of 70.1%.

IR(Neat)cm^{-1} : 1740, 1690, 1550
NMR($CDCl_3$) δ : 1.75-1.88(3H,m), 2.45-2.85(2H,m), 2.90-3.15(2H,m), 3.21(2H,s), 3.25-4.30(4H,m), 5.24(2H,s), 7.55-8.27(4H,d,J=8Hz)

Reference Example 22-A

3.5g of the compound prepared in Reference Example 15-B was dissolved in 50ml of anhydrous acetonitrile, and 1.8g of carbonyldiimidazole was added to the resulting solution under ice-cooling. The mixture was stirred for 30 minutes and then 21g of triethylamine and 2.5g of glycinamide hydrochloride were added thereto. The reaction mixture was stirred for 2 hours under ice-cooling and then 11 hours at room temperature. The reaction solution was diluted with ethyl acetate, washed with distilled water, 1N-hydrochloric acid solution, 5% sodium bicarbonate solution and saline, respectively, dried and then concentrated under reduced pressure. The residue was subjected to column chromatography eluting with ethyl acetate: n-hexane (10:1) to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-{(hydroxycarbonylmethylcarbamoyl)methylcarbamoylethylthiomethyl}-4-(t-butyldimethylsilyloxy)]pyrrolidine in the yield of 65%.

IR(Neat)cm^{-1} : 2250, 1725-1710, 1690-1665
NMR($CDCl_3$) δ : 0.07(6H,s), 0.09(9H,s), 1.27-1.31(4H,m), 2.25-2.60(4H,m), 3.95-4.45(2H,m), 5.25(2H,s), 7.5-8.25(4H,d,J=8Hz)

Reference Example 22-B

4.2g of the compound prepared in Reference Example 22-A

was dissolved in 50ml of anhydrous acetonitrile solution, and 2.5g of carbonyldiimidazole was added to the resulting solution under ice-cooling. The mixture was stirred for 30 minutes. To this mixture were added 21g of triethylamine and 2.06g of 4-aminohydroxyethylpiperazine, and the whole mixture was stirred for 2 hours under ice-cooling and then 10 hours at room temperature. The reaction solution was diluted with ethyl acetate, washed with distilled water, 1N hydrochloric acid solution, 5% sodium bicarbonate solution and saline, respectively, dried and then concentrated under reduced pressure. The residue was subjected to column chromatography eluting with ethyl acetate to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-{(hydroxyethylpiperazinylcarbamoylmethylcarbamoyl)ethylthiomethyl}-4-(t-butyldimethylsilyloxy)]pyrrolidine in the yield of 52%.

IR(Neat)cm^{-1} : 1730, 1710, 1680, 1510

NMR($CDCl_3$) δ : 0.07(6H,s), 0.09(9H,s), 1.25-1.65(4H,m), 2.25-2.45(4H,m), 3.01-3.75(4H,m), 4.15-4.25(2H,m), 5.25(2H,s), 7.55-8.52(4H,d, J=8Hz)

Reference Example 22-C

To 10ml of acetic anhydride were added 2.6g of the compound prepared in Reference Example 22-B and 2.5g of triethylamine and the mixture was stirred for 5 hours under reflux. The reaction solution was evaporated under reduced pressure. The residue was dissolved in ethyl acetate, washed successively with 1N-hydrochloric acid solution, 5% sodium bicarbonate solution and distilled water, dried and then distilled under reduced pressure. The residue was subjected to column chromatography eluting with ethyl acetate to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-{(acetyloxyethylpiperazinylcarbamoylmethylcarbamoyl)ethylthiomethyl}-4-(hydroxy)]pyrrolidine

in the yield of 78.2%.

IR(Neat)cm^{-1} : 1725, 1710-1690, 1610, 1580
NMR($CDCl_3$) δ : 0.07(6H,s), 0.09(9H,s), 1.25-1.30(2H,m), 1.85-2.20(6H,m), 4.15-4.50(4H,m), 3.77-3.90(2H,m), 4.55-4.50(2H,m), 5.24 (2H,d,J=6Hz), 7.65-8.25(4H,d,J=8Hz)

Reference Example 22-D

2.55g of the compound prepared in Reference Example 22-C was dissolved in 30ml of anhydrous dichloromethane, and 0.61g of methanesulfonyl chloride and 0.71g of triethylamine were added to the resulting solution while stirring under ice-cooling. The mixture was then stirred for 2 hours at the same temperature. The reaction solution was washed with distilled water, 1N hydrochloric acid solution and saline, dried and concentrated under reduced pressure to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-{(acetyloxypiperazinylcarbamoylmethylcarbamoyl)ethylthiomethyl}-4-(mesyloxy)]pyrrolidine in the yield of 80.5%.

IR(Neat)cm^{-1} : 1710, 1690, 1510
NMR($CDCl_3$) δ : 2.10-2.45(6H,m), 3.03(3H,m), 5.25(2H,s), 7.53-8.24(4H,d,J=8Hz)

Reference Example 22-E

To 20ml of dimethylformamide was added 1.5g of the compound prepared in Reference Example 22-D and then 0.45g of potassium thioacetate was added thereto. The reaction mixture was stirred for 4 hours at 70 to 80°C, cooled to room temperature, diluted with ethyl acetate, washed several times with distilled water, dried and then concentrated under reduced pressure. The residue was subjected to column

chromatography eluting with ethyl acetate to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-{(acetyloxyethylpiperazinylcarbamoylmethylcarbamoyl)ethylthiomethyl}-4-(acetylthio)]pyrrolidine in the yield of 65.9%.

IR(Neat)cm^{-1} : 1725, 1690, 1420, 1350
NMR($CDCl_3$) δ : 2.15-3.00(6H,m), 3.21(2H,m), 3.75-4.50 (4H,m), 5.23(2H,s), 7.59-8.23(4H,d,J=8Hz)

Reference Example 22-F

2.5g of the compound prepared in Reference Example 22-E was dissolved in 18ml of methanol, and 0.31g of sodium methoxide was added to the resulting solution while stirring under ice-cooling. The reaction mixture was then treated in the same manner as that of Reference Example 15-G to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-{(hydroxyethylpiperazinylcarbamoylmethylcarbamoyl)ethylthiomethyl}-4-(mercapto)]pyrrolidine in the yield of 60.1%.

IR(Neat)cm^{-1} : 1710, 1695, 1520, 1425, 1350
NMR($CDCl_3$) δ : 1.65-1.75(3H,m), 2.45-2.85(4H,m), 2.90-3.30(5H,m), 3.30(2H,s), 5.24(2H,s), 7.55-8.25(4H,d,J=8Hz)

Reference Example 23-A

10g of (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-{(2-hydroxymethylcarbamoyl)ethylmercaptomethyl}-4-acetylthiopyrrolidine was dissolved in 30ml of anhydrous ethyl acetate, and 5ml of trichloroisocyanate was added dropwise to the resulting solution while stirring with ice-cooling under nitrogen atmosphere. The mixture was continuously stirred for 3 hours under ice-cooling. Then, the reaction solution was diluted with 50ml of ethyl acetate, washed with aqueous sodium bicarbonate solution, distilled water and saline,

respectively, and then dried. The residue was subjected to column chromatography eluting with ethyl acetate:n-hexane(4:1) to obtain the desired product (2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-{(2-trichloroacetylaminocarbonyloxymethylcarbamoly)ethymercaptomethyl}-4-acetylthiopyrrolidine in the yield of 52%.

IR(Neat)cm^{-1} : 1755-1750, 1725, 1680, 1600, 1400, 1335
NMR($CDCl_3$) δ : 1.70-1.95(3H,m), 2.45-2.85(1H,m), 2.90-3.15(2H,m), 3.25-3.50(2H,m), 5.24-5.27 (2H,s), 7.55-8.27(4H,d,J=8Hz)

Reference Example 23-B

800mg of the compound prepared in Reference Example 23-A was dissolved in 5ml of methanol, and 3ml of 1N-sodium hydroxide solution was added dropwise to the resulting solution while stirring under ice-cooling. The reaction mixture was stirred for 20 minutes under nitrogen atmosphere, adjusted to the neutral pH value with 1N hydrochloric acid solution, and then concentrated under reduced pressure. The residue was dissolved in ethyl acetate, washed with saline and distilled water, respectively, dried and then concentrated under reduced pressure to obtain an oily residue. The resulting oily residue was subjected to column chromatography eluting with ethyl acetate:n-hexane (5:1) to obtain the desired product (2S,4S)-[1-(p-nitrobenzyloxycarbonyl)-2-{(2-aminocarbonyloxymethylcarbamoyl)ethylmercaptomethyl}-4-mercaptopyrrolidine in the yield of 65%.

IR(Nujol)cm^{-1} : 1715, 1603, 1512, 1398, 1360
NMR($CDCl_3$) δ : 1.65-1.95(3H,m), 2.45-2.95(2H,m), 3.01-3.20(3H,m), 3.25-3.50(2H,m), 3.84-4.30(2H,m), 5.24(2H,s), 7.55-8.27 (4H,d,J=8Hz)

Reference Example 24-A

To 21ml of anhydrous N,N-dimethylformamide were added 2g of (2S,4R)-1-(p-nitrobenzyloxycarbonyl)-2-{(2-iodomethylcarbamoyl)ethylmercaptomethyl}-4-acetylthiopyrrolidine and 1.2g of potassium phthalimide. The mixture was stirred for 6 hours at 90 to 95°C. The reaction solution was diluted with 50ml of distilled water and then extracted three times with 50ml of ethyl acetate in each time. The organic layers were combined, washed with saline and distilled water, respectively, dried and then concentrated under reduced pressure. The residue was subjected to column chromatography eluting with ethyl acetate:n-hexane (2:1) to obtain the desired product (2S,4R)-2-(p-nitrobenzyloxycarbonyl)-2-{(2-phthalimidoylmethylcarbamoyl)ethylmercaptomethyl}-4-acetylthiopyrrolidine in the yield of 72%.

IR(Neat)cm^{-1} : 1775, 1720, 1605, 1522, 1346, 1275
NMR($CDCl_3$) δ : 2.28(3H,s), 2.77(3H,s), 5.18(2H,s), 7.46(2H,d,J=8Hz), 8.16(2H,d,J=8Hz)

Reference Example 24-B

To 20ml of anhydrous ethanol were added 2.5g of the compound prepared in Reference Example 24-A and 2.3g of hydrazine hydrate. The reaction mixture was stirred for about one hour under reflux and then cooled to room temperature. The mixture was filtered to remove the insoluble solid materials and then the filtrate was concentrated. The residue was dissolved in 30ml of anhydrous tetrahydrofuran, and 2.1g of trichloroacetylisocyanate was added to the resulting solution while stirring under ice-cooling. The mixture was stirred for 3 hours and then evaporated under reduced pressure to remove the reaction solvent. The residue was subjected to column chromatography eluting with ethyl acetate:n-hexan (3:1) to obtain the desired product

(2S,4R)-1-(p-nitrobenzyloxycarbonyl)-2-{(2-trichloroacetylaminocarbonylaminomethylcarbamoyl)ethylmercaptomethyl}-4-acetylthiopyrrolidine in the yield of 58%.

IR(Neat)cm^{-1} : 1710, 1600, 1517, 1440, 1270

Reference Example 24-C

860mg of the compound prepared in Reference Example 24-B was dissolved in 10ml of anhydrous methanol, and 1.48ml of 1N-sodium hydroxide solution was added dropwise to the resulting solution while stirring under ice-cooling. The reaction mixture was stirred for 2 hours at room temperature, neutralized with 1.5ml of 1N-hydrochloric acid solution, and then concentrated under reduced pressure. The residue was diluted with 60ml of ethyl acetate, washed with distilled water and then concentrated again under reduced pressure. The residue was subjected to column chromatography eluting with ethyl acetate:n-hexane (1:1) to obtain the desired product (2S,4R)-1-(p-nitrobenzyloxycarbonyl)-2-{(2-aminocarbonylaminomethylcarbamoyl)ethylmercaptomethyl}-4-mercaptopyrrolidine in the yield of 55%.

IR(Neat)cm^{-1} : 1710, 1665, 1590, 1510, 1425

NMR($CDCl_3$) δ : 1.75-1.95(3H,m), 2.45-2.8(1H,m), 2.90-3.15(2H,m), 3.21(2H,s), 3.25-3.50(2H,m), 3.84-4.30(2H,m), 5.24(2H,m), 7.55-8.27(4H,d,J=8Hz)

Reference Example 25-A

To 25ml of anhydrous ethanol was added 1.05g of the compound prepared in Reference Example 24-A. Then, 15ml of saturated ammonia-methanol solution in anhydrous methanol was added thereto. The reaction mixture was stirred for 8 hours under reflux and concentrated under reduced pressure.

The residue was diluted with ethyl acetate, washed with saline and distilled water, respectively, and then concentrated under reduced pressure. The residue was subjected to column chromatography eluting with ethyl acetate:n-hexane (3:1) to obtain the desired product (2S,4R)-1-(p-nitrobenzyloxycarbonyl)-2-{(2-aminomethylcarbamoyl)ethylmercaptomethyl}-4-acetylmercaptopyrrolidine in the yield of 82%.

IR(Neat)cm^{-1} : 1715, 1603, 1512, 1400-1390
NMR($CDCl_3$) δ : 2.28-2.68(1H,m), 3.03-3.70(8H,m), 3.80-4.24(2H,m), 5.16(2H,s), 7.49-8.17 (4H,d,J=8Hz)

Reference Example 25-B

To 15ml of anhydrous methylene chloride was added 610mg of the compound prepared in Reference Example 25-A. While stirring under ice-cooling, 500mg of p-nitrobenzyloxy carbonylchloroformate and 400mg of triethylamine were added to the mixture. The reaction mixture was stirred for 2 hours and then diluted with 30ml of methylene chloride, washed with 1N-hydrochloric acid solution, 10% sodium carbonate solution and distilled water, respectively, dried and then concentrated under reduced pressure. The residue was subjected to column chromatography eluting with ethyl acetate:n-hexane (4:1) to obtain the desired product (2S, 4R)-1-(p-nitrobenzyloxycarbonyl)-2-{(2-nitrobenzyloxycarbonylaminomethylcarbamoyl)ethylmercaptomethyl}-4-acetylthiopyrrolidine in the yield of 75%.

IR(Neat)cm^{-1} : 1760, 1715, 1690, 1550, 1480
NMR($CDCl_3$) δ : 2.40-3.10(5H,m), 3.15-3.60(2H,m), 5.15-5.35(4H,m), 7.35-7.70(7H,m), 7.75-8.15 (2H,m), .8.22(4H,br.J=8Hz)

Reference Example 25-C

710mg of the compound prepared in Reference Example 25-B was dissolved in 10ml of anhydrous methanol and this reaction mixture was treated in the same manner as that of Reference Example 24-C to obtain the desired product (2S, 4R)-1-(p-nitrobenzyloxycarbonyl)-2-{(4-nitrobenzyloxycarbonylaminomethylcarbamoyl)ethylmercaptomethyl}-4-mercaptopyrrolidine in the yield of 55%.

IR(Neat)cm^{-1} : 1710-1700, 1610, 1530-1520, 1350
NMR($CDCl_3$) δ : 1.60-2.00(2H,m), 2.30-3.65(8H,m), 3.80-4.35(2H,m), 5.20(4H,s), 7.50-7.55 (4H,d,J=8Hz), 8.21(4H,d,J=8Hz)

Reference Example 26-A

1.3g of (2S,4R)-1-(p-nitrobenzyloxycarbonyl)-2-{(2-hydroxymethylcarbamoyl)ethylmercaptomethyl}-4-acetylthiopyrrolidine was added to 30ml of anhydrous methylene chloride. To this reaction mixture were added 2ml of a solution of diazomethane dissolved in ethyl ether and a catalytic amount of boron trifluoride-etherate complex while stirring under ice-cooling, and then the whole mixture was stirred for 30 minutes. The reaction solution was washed with saline and filtered to remove the insoluble solid materials. The filtrate was washed with aqueous sodium bicarbonate solution, saline and distilled water, respectively. The organic layer was separated and concentrated under reduced pressure. The residue was subjected to column chromatography eluting with ethyl acetate:n-hexane (10:1) to obtain the desired product (2S,4R)-1-[(p-nitrobenzyloxycarbonyl)-2-{(methoxymethylcarbamoyl)ethylmercaptomethyl}-4-acetylmercaptopyrrolidine in the yield of 62%.

IR(Neat)cm^{-1} : 1710, 1690, 1685, 1520, 1390
NMR($CDCl_3$) δ : 2.46-2.95(2H,m), 3.15(3H,s), 3.85-4.15 (3H,m), 5.16(2H,s), 7.49-8.17(4H,br.J=8Hz)

Reference Example 26-B

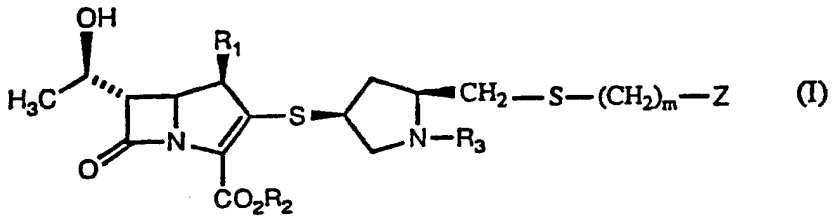
910mg of the compound prepared in Reference Example 26-A was added to 15ml of anhydrous methanol, and the reaction mixture was treated in the same manner as that of Reference Example 24-C to obtain the desired product (2S,4R)-1-(p-nitrobenzyloxycarbonyl)-2-{(methoxymethylcarbamoyl)ethylmercaptomethyl}-4-mercaptopyrrolidine in the yield of 50%.

IR(Neat)cm^{-1} : 1710-1700, 1690-1680, 1550-1540, 1390

NMR($CDCl_3$) δ : 1.60-2.05(2H,m), 2.33-3.10(2H,m), 3.15 (3H,s), 3.30-3.80(5H,m), 3.85-4.33(2H,m), 5.24(2H,s), 7.56-8.26(2H,d,J=8Hz)

WHAT IS CLAIMED IS :

1. 2-(2-Substituted pyrrolidin-4-yl)thio-carbapenem derivative represented by the following general formula (I):



(I)

and pharmaceutically acceptable salts thereof, in which

R_1 represents hydrogen or (lower)alkyl,

R_2 represents hydrogen or anion,

R_3 represents hydrogen or (lower)alkanimidoyl.

Z represents $-\overset{X}{\overset{\|}{C}}-R_4$ or R_9,

X represents O or NH,

R_4 represents amino or heterocyclic amine group, each of which can be unsubstituted or substituted with a group of formula $-CH\begin{matrix}R_5\\R_6\end{matrix}$, a unsubstituted or substituted heterocyclic group or a lower alkyl group, or represents hydroxy(lower)alkyl or carbamoyloxy(lower)alkyl,

R_5 and R_6 independently of one another represent hydrogen, hydroxy, hydroxy(lower)alkyl, cyano, amino, carbamoyl, carbamoyl(lower)alkyl, cyano(lower)alkyl, mono-or di-(lower)alkylcarbamoyl, carbamoyloxy, ureido, amino-(lower)alkyl, carbamoyloxy(lower)alkyl, mono-or di-(lower)alkylcarbamoyl(lower)alkyl, ureido(lower)alkyl, or a group of formula $-CO-N\bigcirc$ or $-CH_2CO-N\bigcirc$ wherein $-N\bigcirc$ denotes a unsubstituted or substituted 3- to 6-membered heterocyclic group which can contain additional hetero atoms, provided that R_5 and R_6 cannot be hydrogen at the same time,

R_9 represents hydroxy(lower)alkyl or carbamoyloxy, and m is an integer of 1 to 6, provided that when m is 1 and X is O, R_4 is other than unsubstituted amino($-NH_2$).

2. The compound of claim 1, wherein R_1 represents hydrogen or lower alkyl, R_2 represents hydrogen or anion, R_3 represents hydrogen or straight or branched (C_1-C_6)alkanimidoyl, Z represent $-\overset{O}{\overset{\|}{C}}-R_4$ or R_9, R_4 represents $-NHCH\begin{matrix}R_5\\R_6\end{matrix}$, wherein R_5 and R_6 independently of one another represent hydrogen, hydroxy, hydroxy(lower)alkyl, CN, carbamoyl-(lower)alkyl, cyano(lower)alkyl, carbamoyloxy(lower)alkyl, ureido(lower)alkyl or substituted or unsubstituted piperazinylprovided that R_5 and R_6 cannot be hydrogen at the same time, R_9 represents hydroxy(C_1-C_6)alkyl or carbamoyloxy and m is an interger of 1 to 4.

3. The compound of claim 2, wherein R_1 represents methyl, R_2 represents hydrogen, R_3 represents hydrogen or acetimidoyl, Z represents $-\overset{O}{\overset{\|}{C}}-R_4$ or R_9, R_4 represents $-NHCH\begin{matrix}R_5\\R_6\end{matrix}$, wherein R_5 and R_6 independently of one another represent hydrogen, hydroxy, hydroxy(C_1-C_4)alkyl, cyano, cyano(C_1-C_4)alkyl, carbamoyloxy(C_1-C_4)alkyl, ureido(C_1-C_4)alkyl, or piperazinyl optionally mono-substituted with substituent selected from carbamoyl, (C_1-C_4)alkyl, hydroxy(C_1-C_4)alkyl, cyano(C_1-C_4)alkyl, amino(C_1-C_4)alkyl, carbamoyloxy(C_1-C_4)alkyl, ureido(C_1-C_4)alkyl, carbamoyl(C_1-C_4)alkyl and mono- or di(C_1-C_4)alkylcarbamoyl(C_1-C_4)alkyl provided that R_5 and R_6 cannot be hydrogen at the same time, R_9 represents hydroxy(C_1-C_4)alkyl or carbamoyloxy and m is an integer of 1 to 2.

4. The compound of claim 1, which is selected from

the group consisting of :

-(1R,5S,6S)-2-[(2S,4S)-2-{(cyanomethylcarbamoyl)methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{(cyanomethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{(aminoethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{(carbamoylmethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{(hydroxyethylcarbamoyl)methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{(carbamoylmethylcarbamoyl)methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{(cyanoethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{(hydroxyethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{(carbamoylethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-1-acetimidoyl-2-{(2-carbamoylethylcarbamoyl)methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-1-acetimidoyl-2-{(2-carbamoylmethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{(1,2-dihydroxyethylcarbamoyl)methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{(1-hydroxy-2-cyanoethylcarbamoyl) methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{(1-hydroxy-2-aminoethylcarbamoyl) methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{(1-hydroxy-2-carbamoylethylcarbamoyl)methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{(1,2-dihydroxyethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{(1-hydroxy-2-cyanoethylcarbamoyl)-ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{(1-hydroxy-2-carbamoylethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{(1-(hydroxymethyl)-2-hydroxyethylcarbamoyl)methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{(1-(hydroxymethyl)-2-carbamoylethylcarbamoyl)methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{(1-(hydroxymethyl)-2-carbamoylethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{(1-(carbamoylmethyl)-2-ureidoethylcarbamoyl)methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{(1-(carbamoylmethyl)-2-cyanoethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

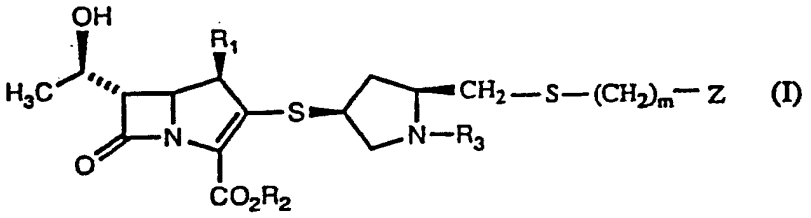
-(1R,5S,6S)-2-[(2S,4S)-2-{(1-(carbamoylmethyl)-2-aminoethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-

1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{(2-ureidoethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{(N-methylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{(N,N-dimethylcarbamoyl)methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{1-acetimidoyl-2-(carbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{1-acetimidoyl-2-(N-methylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{(N-(2-hydroxyethyl)-piperazinylcarbonyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{(N-(2-carbamoyloxyethyl)-piperazinylcarbonyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{(N-(2-aminoethyl)-piperazinylcarbonyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{(2-hydroxyethyl)mercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{(3-hydroxypropyl)mercaptomethyl}-pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{(3-(carbamoyloxy)propyl)mercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{2-(hydroxyethylpiperidinylcarbonylmethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxy-

lic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{2-(aminoethylpiperidinylcarbonylmethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{2-(methoxyethylpiperidinylcarbonylmethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{2-(carbamoyloxyethylpiperidinylmethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{2-(ureidoethylpiperidinylmethyl carbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{2-(methoxymethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{2-(carbamoyloxymethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{2-(ureidomethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{2-(methoxymethyloxymethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{2-(aminomethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{2-(cyanoethylpiperidinylcarbonylmethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-2-{2-(methylcarbamoyloxymethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

-(1R,5S,6S)-2-[(2S,4S)-2-{2-(methoxymethyloxyethylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
-(1R,5S,6S)-2-[(2S,4S)-1-formimidoyl-2-{(hydroxyethylcarbonyl)methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid, and
-(1R,5S,6S)-2-[(2S,4S)-2-{(carbamoylethyl)mercaptomethyl}pyrrolidin-4-yl]thio-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid.

5. A process for preparation of compound of formula (I) :



(I)

and salts thereof, in which

R_1 represents hydrogen or (lower)alkyl,

R_2 represents hydrogen or anion,

R_3 represents hydrogen or (lower)alkanimidoyl,

Z represents $-\overset{\overset{X}{\|}}{C}-R_4$ or R_9,

X represents O or NH,

R_4 represents amino or heterocyclic amino group, each of which can be unsubstituted or substituted with a group of formula $-CH\begin{matrix}R_5\\R_6\end{matrix}$, a unsubstituted or substituted heterocyclic group or a (lower)alkyl group, or represents hydroxy(lower)alkyl or carbamoyloxy(lower)alkyl,

R_5 and R_6 independently of one another represent hydrogen, hydroxy, hydroxy(lower)alkyl, cyano, amino, carbamoyl, carbamoyl(lower)alkyl, cyano(lower)alkyl, mono- or di-(lower)alkylcarbamoyl, carbamoyloxy, ureido, amino-(lower)alkyl, carbamoyloxy(lower)alkyl, mono- or di-(lower)alkylcarbamoyl(lower)alkyl, ureido(lower)alkyl,

or a group of formula -CO-N◯ or -CH_2CO-N◯ wherein -N◯ denotes a unsubstituted or substituted 3- to 6-membered heterocyclic group which can contain additional hetero atoms, provided that R_5 and R_6 cannot be hydrogen at the same time,

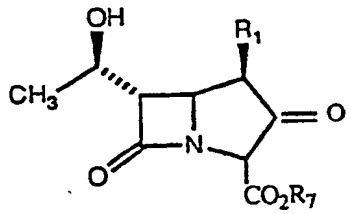
R_9 represents hydroxy(lower)alkyl or carbamoyloxy, and

m is an integer of 1 to 6, provided that

when m is 1 and X is O, R_4 is other than unsubstituted amino(-NH_2),

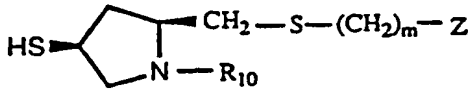
which comprises

1) reacting a compound of formula(II) :



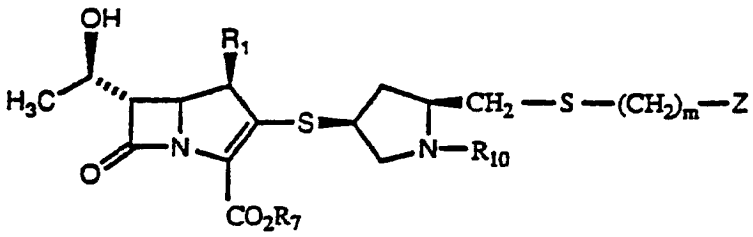
(II)

wherein R_1 is as defined above and R_7 represents a carboxy-protecting group, or a reactive derivative at the oxo group thereof or salts thereof with a mercaptopyrrolidine derivative of formula(III) :



(III)

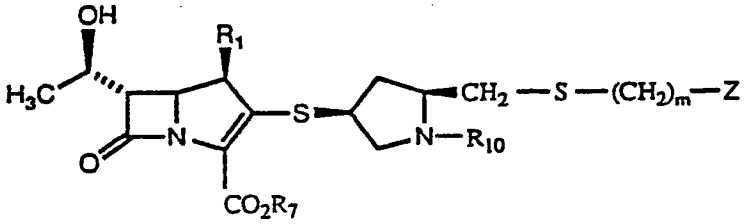
wherein Z and m are as defined above and R_{10} represents and imino-protecting group, or salts thereof to obtain a compound of formula(IV) :



(IV)

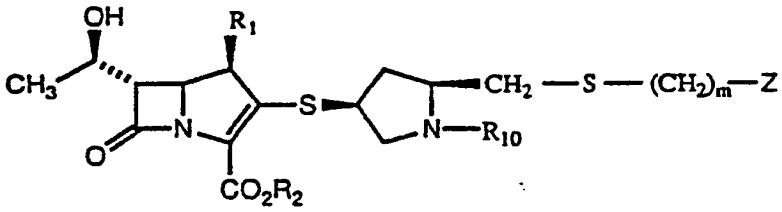
wherein R_1, R_7, R_{10}, Z and m are as defined above, or salts thereof,

2) subjecting a compound of formula(IV) :



(IV)

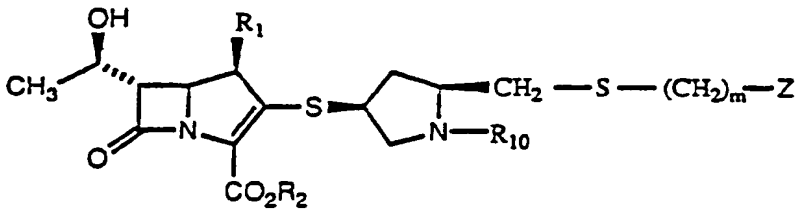
wherein R_1, R_7, R_{10}, Z and m are as defined above, or salts thereof to elimination reaction of the carboxy-protecting group to provide a compound of formula(I-a),



(I-a)

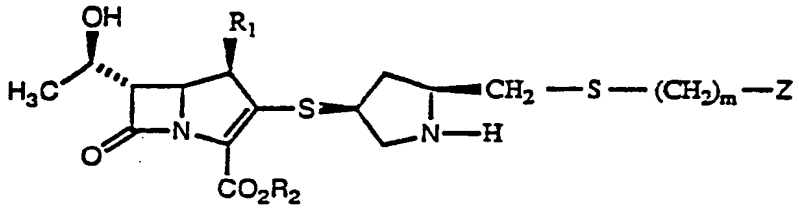
wherein R_1, R_2, R_{10}, Z and m are as defined above, or salts thereof :

3) subjecting a compound of formula(I-a) :



(I-a)

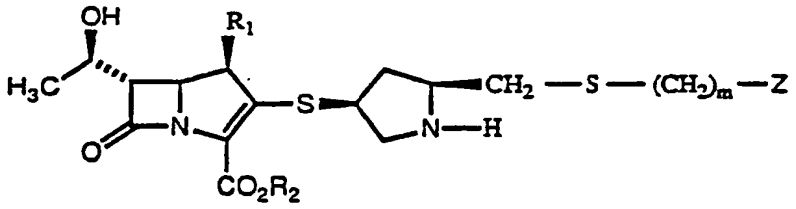
wherein R_1, R_2, R_{10}, Z and m are as defined above, or salts thereof to elimination reaction of the imino-protecting group to provide a compound of formula(I-b):



(I-b)

wherein R_1, R_2, Z and m are as defined above, or salts thereof,

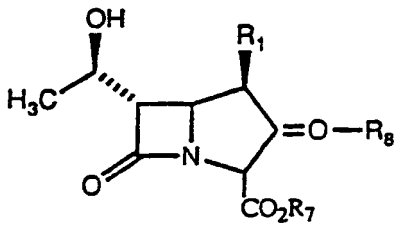
4) if necessary, reacting a compound of formula(I-b) :



(I-b)

wherein R_1, R_2, Z and m are as defined above, or salts thereof with a lower alkanimidoylating agent to provide the compound of formula(I) wherein R_3 is lower alkanimidoyl or salts thereof.

6. The process of claim 5, wherein in Process 1 the reactive derivative of the compound of formula(II) is a compound of the following formula(II-a) :

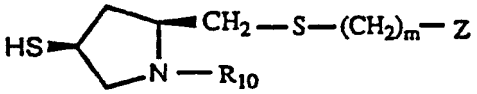


(II-a)

wherein R_1 and R_7 are as defined above and R_8 represents acyl group or O,O-substituted phosphono group derived from organic phosphoric acid.

7. The process of claim 5, wherein in Processes 2 and 3 the elimination of protecting groups is carried out by means of hydrolysis or reduction.

8. A mercaptopyrrolidine derivative represented by the following general formula(III) :



(III)

or salts thereof, in which

R_{10} represents an imino-protecting group,

Z represents $-\overset{X}{\overset{\|}{C}}-R_4$ or R_9,

X represents O or NH,

R_4 represents amino or heterocyclic amine group, each of which can be unsubstituted or substituted with a group of formula $-CH\begin{matrix}R_5\\R_6\end{matrix}$, a unsubstituted or substituted heterocyclic group or a (lower)alkyl group, or represents hydroxy(lower)alkyl or carbamoyloxy (lower)alkyl,

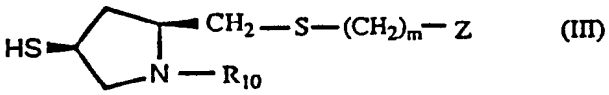
R_5 and R_6 independently of one another represent hydrogen, hydroxy, hydroxy(lower)alkyl, cyano, amino, carbamoyl, carbamoyl(lower)alkyl, cyano(lower)alkyl, mono- or di-(lower)alkylcarbamoyl, carbamoyloxy, ureido, amino(lower) alkyl, carbamoyloxy(lower)alkyl, mono- or di-(lower)alkylcarbamoyl(lower)alkyl, ureido(lower)alkyl, or a group of formula -CO-N◯ or -CH_2CO-N◯ wherein -N◯ denotes a unsubstituted or substituted 3-to 6-membered heterocyclic group which can contain additional hetero atoms, provided that R_5 and R_6 cannot be hydrogen at the same time,

R_9 represents hydroxy(lower)alkyl or carbamoyloxy, and

m is an interger of 1 to 6, provided that

when m is 1 and X is O, R_4 is other than unsubstituted amino(-NH_2).

9. A process for preparing compounds of formula(III):



(III)

or salts thereof, in which

R_{10} represents an imino-protecting group,

Z represents $-\overset{\overset{X}{\|}}{C}-R_4$ or R_9,

X represents O or NH,

R_4 represents amino or heterocyclic amine group, each of which can be unsubstituted or substituted with a group of formula $-CH\begin{matrix}R_5\\R_6\end{matrix}$, a unsubstituted or substituted heterocyclic group or a (lower)alkyl group, or represents hydroxy(lower)alkyl or carbamoyloxy(lower)alkyl,

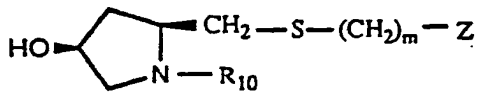
R_5 and R_6 independently of one another represent hydrogen, hydroxy, hydroxy(lower)alkyl, cyano, amino, carbamoyl, carbamoyl(lower)alkyl, cyano(lower)alkyl, mono- or di-

(lower)alkylcarbamoyl, carbamoyloxy, ureido, amino(lower)alkyl, carbamoyloxy(lower)alkyl, mono- or di-(lower)alkylcarbamoyl(lower)alkyl, ureido(lower)alkyl, or a group of formula -CO-N◯ or -CH_2CO-N◯ wherein -N◯ denotes a unsubstituted or substituted 3- to 6-membered heterocyclic group which can contain additional hetero atoms, provided that R_5 and R_6 cannot be hydrogen at the same time,

R_9 represents hydroxy(lower)alkyl or carbamoyloxy, and

m is an interger of 1 to 6, provided that when m is 1 and X is O, R_4 is other than unsubstituted amino(-NH_2), which comprises

A) reacting a compound of formula(V) :

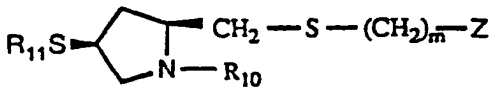


(V)

wherein R_{10}, Z and m are as defined above, or a reactive derivative at the hydroxy group thereof or salts thereof with a compound of formula(VI),

$$R_{11}\text{-SH} \qquad \text{(VI)}$$

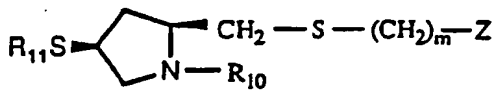
wherein R_{11} represents a mercapto-protecting group, or salts thereof to provide a compound of formula(III-a),



(III-a)

wherein R_{10}, R_{11}, Z and m are as defined above, or salts thereof; and

B) subjecting a compound of formula(III-a),



(III-a)

wherein R_{10}, R_{11}, Z and m are as defined above, or salts thereof to elimination reaction of the mercapto-protecting group.

10. An antibacterial composition comprising, as an active ingredient, at least one of the compound(I) as defined in any one of claims 1 to 4 and pharmaceutically acceptable salts thereof.

11. Use of the compound (I) as defined in any one of claims 1 to 4 and pharmaceutically acceptable salts thereof as an antibacterial agent.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 93/00114

A. CLASSIFICATION OF SUBJECT MATTER
IPC[5]: C 07 D 477/00, 207/12; A 61 K 31/40, 31/445, 31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[5]: C 07 D 477/00, 207/00; A 61 K 31/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP, A1, 0 280 771 (FUJISAWA PHARMACEUTICAL CO., LTD) 07 September 1988 (07.09.88), claims 1,2,4,5,15-18,20, 21; examples 2,4.	1-3,5,8-11
A	EP, A1, 0 182 213 (SUMITOMO PHARMACEUTCALS COMPANY LIMITED) 28 May 1986 (28.05.86), claims 1,2,6,7,9; pages 33-34, table 4, compound no. 15; pages 94-105, table 12, compound no. 33; pages 115-125, table 14, compounds no. 211-214.	1-4,8,9,23,24
A	EP, A2, 0 243 686 (SUMITOMO PHARMACEUTICALS COMPANY LIMITED) 04 November 1987 (04.11.87), claims 1-4,6,14, 15,17,18; pages 8-11,39; pages 19-27, table 1, compounds no. 189-192.	1-3,5-7,10,11
A	CH, A5, 657 853 (SANKYO COMPANY LIMITED) 30 September 1986 (30.09.86), claims 1-8, 11-14, 16, 20, 21, 25; page 7, right column, lines 3-9.	1-3,5-8,10,11

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
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"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
04 March 1994 (04.03.94)	22 March 1994 (22.03.94)

Name and mailing address of the ISA/ AT	Authorized officer
AUSTRIAN PATENT OFFICE Kohlmarkt 8-10 A-1014 Vienna	Mazzucco e.h.
Facsimile No. 1/53424/535	Telephone No. 1/5337058/33

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/KR 93/00114

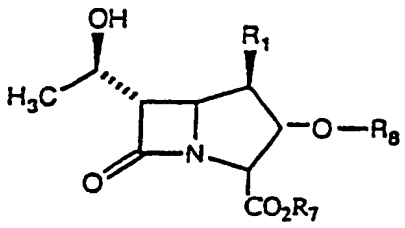
Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
EP A1 280771	07-09-88	AT E 87628	15-04-93
		AT E 92068	15-08-93
		AU A1 81500/87	26-05-88
		AU B2 599439	19-07-90
		CN A 87107938	10-08-88
		DE C0 3785163	06-05-93
		DE T2 3785163	29-07-93
		DE C0 3786781	02-09-93
		DE T2 3786781	25-11-93
		DK A0 5946/87	12-11-87
		DK A 5946/87	25-05-88
		EP A1 272456	29-06-88
		EP B1 272456	31-03-93
		EP B1 280771	28-07-93
		FI A0 875135	20-11-87
		FI A 875135	25-05-88
		GB A0 8716937	26-08-87
		IL A0 84446	29-04-88
		JP A2 63179875	23-07-88
		JP A2 63179876	23-07-88
		NO A0 874869	23-11-87
		NO A 874869	25-05-88
		NZ A 222634	26-06-90
		PT A 86182	01-12-87
		PT B 86182	07-11-90
		US A 4822787	18-04-89
		US A 4963543	16-10-90
		US A 5061804	29-10-91
		GB A0 8709399	28-05-87
		GB A0 8631081	04-02-87
		GB A0 8628063	31-12-86
		ZA A 8708287	29-06-88
EP A1 182213	28-05-86	AT E 56974	15-10-90
		CA A1 1281720	19-03-91
		DE C0 3579888	31-10-90
		EP B1 182213	26-09-90
		ES A1 548728	16-06-87
		ES A5 548728	13-07-87
		ES A1 8706684	16-09-87
		US A 4962103	09-10-90
		JP A2 62155279	10-07-87
		JP B4 5029229	28-04-93
EP A2 243686	04-11-87	AT E 78255	15-08-92
		DE C0 3780344	20-08-92
		DE T2 3780344	28-01-93
		EP A3 243686	02-03-88
		EP B1 243686	15-07-92
		US A 5093328	03-03-92
		JP A2 1104076	21-04-89
CH A 657853	30-09-86	AT E 18048	15-03-86
		AT E 42952	15-05-89
		AU A1 87207/82	24-02-83
		AU A1 65132/86	19-02-87
		AU B2 563447	09-07-87
		AU B2 582480	23-03-89
		CA A1 1214462	25-11-86
		DE C0 3269183	27-03-86
		DE C0 3279683	15-06-89
		DK A 3706/82	20-02-83
		EP A1 72710	23-02-83
		EP A1 165384	27-12-85
		EP B1 72710	19-02-86
		EP B1 165384	10-05-89
		ES A1 515098	16-10-83
		ES A5 515098	16-11-83
		ES A1 8400444	16-01-84

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/KR 93/00114

FI	AO	822864	18-08-82
FI	A	822864	20-02-83
FI	A	873303	29-07-87
FI	AO	873303	29-07-87
FI	B	76339	30-06-88
FI	C	76339	10-10-88
FI	B	84826	15-10-91
FI	C	84826	27-01-92
FR	A1	2511678	25-02-83
FR	B1	2511678	25-04-86
GB	A1	2104075	02-03-83
GB	AO	8518818	29-08-85
GB	A1	2163156	19-02-86
GB	B2	2104075	29-05-86
GB	B2	2163156	16-07-86
HU	B	189171	30-06-86
IE	B	53736	01-02-89
IE	B	53737	01-02-89
IT	AO	8268024	19-08-82
IT	A	1156491	04-02-87
JP	A2	58032879	25-02-83
JP	B4	61029357	05-07-86
KR	B1	8901426	03-05-89
NO	A	822793	21-02-83
NO	A	875188	21-02-83
NO	AO	875188	14-12-87
NO	B	159656	17-10-88
NO	C	159656	25-01-89
NO	B	167918	16-09-91
NO	C	167918	27-12-91
NZ	A	201633	08-11-85
PH	A	20772	10-04-87
US	A	4552873	12-11-85
ZA	A	8206024	27-07-83
CH	A	659072	31-12-86
DE	A1	3317742	17-11-83
DE	C2	3317742	29-08-91
ES	A1	522389	16-08-84
ES	A5	522389	17-09-84
ES	A1	8407053	16-11-84
ES	A1	528491	01-05-85
ES	A5	528491	31-05-85
ES	A1	8504815	16-07-85
FR	A1	2526798	18-11-83
FR	B1	2526798	04-10-85
GB	AO	8313399	22-06-83
GB	A1	2121792	04-01-84
GB	B2	2121792	08-01-86
IT	AO	8321084	13-05-83
IT	A	1164226	08-04-87
JP	A2	58198486	18-11-83
JP	B4	3018638	13-03-91
US	A	4613595	23-09-86

Formula (II-a) in claim 6 was read as:



(II-a)

It should be corrected in claim 6 (see PCT/ISA/216).

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